RESEARCH PROTOCOL

EFFECTIVENESS OF TOPICAL MENTHOL AS A COOLING METHOD DURING EXERCISE IN A RECREATIONAL RUNNER POPULATION

Research Team:
Specialist Doctors of Sports Medicine
A. Andi Kurniawan, MD
Angelica Anggunadi, MD
Wawan Budisusilo, MD
Albertus Quarino, MD
Monica Surjanto, MD

Work closely with:
PT Taisho Pharmaceutical Indonesia TBK

1. GENERAL INFORMATION

Research Title	: EFFECTIVENESS OF TOPICAL MENTHOL AS A COOLING METHOD DURING EXERCISE IN A POPULATION OF RUNNERS
Clinical Trial Phase	: Pre-Marketing Phase for new Indications
Protocol Version Number	: CTP.Mentol/V004/V/2023
Protocol Version Date	: May 19, 2023
Principal Investigator	: A. Andi Kurniawan, MD (Contact number: +62 878-8839-1980)
Research Team	: Angelica Anggunadi, MD Wawan Budisusilo, MD Albertus Quarino, MD Monica Surjanto, MD
Research Site Coordinator	: Theresia Indriani Prima Chesar, MD (Contact number: +62 812-9583-8147) Nisrina Nindriya, MD (Contact number: +62 812-2173-4814)
Statistical Consultant	: Prof. Dra Arini Setiawati, Ph.D.
Sponsor	: Ni Putu Ardini, MD - PT Taisho Pharmaceutical Indonesia TBK Millenium Centennial Center 8th Floor Jalan Jend. Sudirman Kav. 25 Jakarta, Indonesia (Contact Number: +62 85888337997)
Research site	: Eminence Elite Clinic - Elite Club Jl. Epicentrum Utama Raya Jl.H.R.Rasuna Said No.Kav C 22 Karet Kuningan Kec.Setiabudi, Jakarta, Indonesia
Clinical Trial Location	: GOR Soemantri Athletic Field, Jakarta, Indonesia

2. BACKGROUND INFORMATION

2.1 Products under study

This research will use products produced by PT Taisho Pharmaceutical Indonesia Tbk with the following details:

- Product brand : Counterpain® COOL
- Active substance content: Menthol 4%
- Registration number : POM QD. 111709501
- Approved indications: To relieve pain in muscles due to exercise, sprains, bruises or back pain.
- Proposal indication in this study: Counterpain COOL with COOL Sensation, **as a cooling method when exercising in hot air environments**. And to relieve pain in muscles due to exercise, sprains, bruises or back pain.

2.2 Summary of other relevant clinical trials

Currently, there are no clinical trials using the studied products to support cooling methods during exercise in hot environments in Indonesia. However, in various other countries, clinical trials have been conducted using topical products containing Menthol and the results support the use of menthol as a cooling method during exercise in hot air environments.

In 2018, 17 healthy men (n=17) between the ages of 18 and 35 were recruited to take part in a study conducted by Mitchell Snell (titled "Influence of menthol on human temperature perception, regulation and energy expenditure") at Salem State University. Subjects rested supine in a controlled environment at 30℃ and 50% relative humidity. Subjects rested for 30 minutes before menthol or placebo gel was applied to establish baseline temperature and metabolic values. Placebo gels without menthol and those containing 4.13% Menthol (Biofreeze, Performance Health, Warrenville, IL, USA) were applied to the anterior surface of participants while resting in the supine position at 30 minutes to 60 minutes. Outcomes collected were core body temperature (Tre), RER (*Respiratory Exchange Ratio*), absolute VO_2, relative VO_2, supraclavicular skin temperature, skin blood perfusion, and thermal sensation. Some measures showed no significant response to menthol, however, the reason remains unclear. Two variables that showed significant changes due to menthol application were core body temperature and thermal sensation. Menthol seemed to make the body feel cooler (lower thermal sensation score), but at the same time caused it to store more heat (increased rectal temperature).

Another study conducted by D Jason Gillis, et al (titled "The influence of menthol dose on human temperature regulation and perception") in 2020 assessed the effect of high (H, 4.13%), medium (M, 2.0%) and low (L, 0.1%) concentrations of menthol on temperature perception and regulation, compared to a placebo (P). Sixteen participants underwent the

conditions on four separate days. Each test participant rested supine (Environmental conditions: 30°C, 50% rh) for 30 minutes before 40 mL of L, M, H or P gel was applied to the anterior upper body, then rested 30 minutes thereafter. Primary parameters assessed included thermal sensation (TS), thermal comfort (TC), irritation (IRR), rectal temperature (Tre), skin temperature (chest, forearm, thigh, calf), and EMG (trapezius, pectoralis major, sternocleidomastoid). This study showed that menthol exerts perceptual and thermoregulatory effects regardless of skin temperature. The perceptual cooling effect was also dependent on the concentration of menthol administered, with the greatest effect exhibited by menthol of medium concentration. Changes in core body temperature were also shown to be dependent on menthol concentration.

2.3 Summary of known risks and benefits

Referring to previous clinical trials on menthol gel, it is known that the application of menthol gel influences thermal sensation and changes in core body temperature. The risk of irritation with menthol application may occur depending on the dose administered.

2.4 Description and justification for mode of administration, dosage, dosage regimen and period of administration

The test drug consists of:

- Test Drug
  Light blue gel with the trademark Counterpain COOL® (License Number: POM QD. 111 709 501) containing the active substance Menthol 4%.
- Placebo
  Light blue gel where the active ingredient Menthol is replaced by purified water.

Each Subject will receive a *cross-over* application of 4% Menthol gel and placebo with the order of application *randomized* using a *random number table* and a minimum *wash out* period of 7 days± 1 day after the first application. The test drug, i.e. 4% Menthol gel or placebo, will be applied by rubbing on the neck area, the front side of the upper arm and the front side of the upper leg. The neck area was chosen because there is a carotid artery in the neck area, which is said to have an impact on changes in body temperature in the hypothalamus. In addition, the upper arm and upper leg areas were chosen because they are the extremity areas closest to the core of the body and perform a lot of movement while running. Some journals concluded that the application of cooling methods in the hand and thigh area is effective for cooling methods.
The application is adjusted to the *Per (Mid) Cooling* method, where the Subject will start applying the test drug while running on lap 7 (along kilometer 2.5 to 2.8).

dose of the test drug, 4% Menthol gel or placebo, was administered by following the dosage of topical drugs in general, as follows:[2]

- 2 grams (2.25 inches or 5.7cm) for the neck
- 4 grams (4.5 inches or 11.4cm) for each upper extremity (including upper arm or forearm) and lower extremity

The total dose given is not more than the maximum total dose limit of 32 grams in a day of use.

The test drug dose card consists of 3 dose cards consisting of dose cards for the neck, right and left upper arms, right and left upper limbs.

2.5 Researcher statement

The research team leader and the rest of the research team agree to conduct the study in accordance with the protocol and any amendments and in accordance with current ICH GCP guidelines, be responsible for conducting and supervising the study as a whole, ensure that all associates, colleagues and employees assisting in conducting the study are informed of their obligations, and agree to conduct the study in full compliance with the laws and regulations of the country in which the study is conducted and the Declaration of Helsinki.

2.6 Population description

The subjects of this study were recreational runners who were trained and selected from running clubs aged 18-45 years, domiciled in Jakarta and its surroundings, and met the inclusion criteria and did not have exclusion criteria. The recreational runners selected from this running club were runners who already had the experience of completing a marathon before by providing certificates/medals/other evidence. And had a *personal best of* under one hour on a 10-kilometer run (which would be confirmed during the screening of potential subjects through history taking) in the past 6 months.

2.7 Literature reference

Exposure to heat during exercise causes an increase in body temperature (core and skin temperature), impaired thermal perception (sensation and comfort), and dehydration that will affect the cardiovascular system, central nervous system, and musculoskeletal function. This results in impaired sports performance. Over the past few decades, various cooling techniques have been developed with the aim of offsetting exercise-induced increases in core body temperature and improving thermal perception.

Cooling techniques can be divided into internal and external cooling. Internal cooling aims to alleviate *thermal strain* by lowering the core body temperature, such as through the

consumption of cold drinks. While external cooling techniques, such as the use of *cooling garments, cold-water immersion*, or fans, aim to reduce *thermal strain* through increasing the core-to-skin temperature gradient and increasing thermal perception. Both cooling techniques can be combined to provide a greater effect, both physiologically and perceptually.

Cooling interventions can increase heat storage capacity (*pre-cooling*), reduce exercise-induced increases in core body temperature (*mid-cooling*), and accelerate recovery after intense exercise (*post-cooling*). Cooling interventions are known to improve exercise performance, such as *time trial performance* and *time to exhaustion*, in hot environmental conditions (>30^{O}C) or conditions where prolonged exercise is performed.

Mid-cooling interventions aim to reduce the increase in core temperature during exercise. It is known that the effects of *pre-cooling* interventions usually fade by 20-25 minutes after the start of exercise. This suggests that the benefits of *pre-cooling* mostly occur during the initial phase of resistance training. However, exercise intensity, heat production, and *thermal strain* are higher during exercise than at rest or warm-up, thus emphasizing the greater potential ergogenic benefits of *mid-cooling* than *pre-cooling*. The mechanism of improving sports performance through *mid-cooling* by reducing *cardiovascular strain*, lowering skin temperature, improving central nervous system function and increasing thermal perception. The application of *mid-cooling* methods in athletes can extend the duration of the benefits of cooling interventions. *Mid-cooling* effectively increases *time to exhaustion* and is also effective in *self-paced exercise.* Some of the *mid-cooling* methods that can be used include *cooling packs, ice vests*, consumption of cold drinks or *ice slurry*, fans (with or without *mist*), *water spray,* and interventions using menthol in the form of mouthwash, spray, or topical gel. *Ice slurry drinks* are considered the most effective *mid-cooling* method, but consuming large volumes of cold drinks may induce physical complaints such as gastrointestinal distress, nausea, "brain freeze" or headache. The use of *ice vests*, fans, and *water sprays* are also considered effective in laboratory conditions, but are not practical in competition.

Menthol is a non-thermal cooling stimulus that acts on receptors without lowering temperature when applied to the skin and mucosal surfaces.[(4)(7)] Menthol causes a sensation of freshness, coolness, and nasal patency through stimulation of *transient receptor potential melastatin* 8 (TRPM 8) which functions as a cold receptor.[4,20,4(7)(,4)8] Activation of these sensory pathways sends information to the brain thus reducing the perception of *thermal strain* that occurs.

The use of menthol as a cooling intervention during exercise has been widely encountered. Methods used can be internal cooling, such as *mouth rinse* and additives in cold drinks, or external, such as *sprays* and topical gels.[4] Topical application of placebo and *mouth rinse* is ergogenic in endurance exercise in hot environments, improving performance and

perception, with different effects on body temperature regulation. Their use can be through a single application with a high concentration and repeated applications.

3. PURPOSE AND OBJECTIVES OF CLINICAL TRIALS

In general, to determine the effect of topical menthol application as a cooling method when exercising in a hot air temperature environment.

3.1 Primary Objective:

To determine the effect of topical menthol application as a cooling method during exercise by finding out the difference in thermal sensation between the menthol gel topical applied group and placebo.

3.2 Secondary Objectives:

To determine the effect of topical menthol application on various other parameters as a cooling method during exercise, namely by knowing the difference in body temperature, the difference in heart rate frequency and the difference in physical performance and intensity during exercise and also knowing the perception (acceptance) of comfort and irritation scores between the groups applied topical menthol gel and placebo.
In addition, the safety of the drug will also be assessed by finding out all adverse events that occur with topical menthol application and placebo after running.

4. CLINICAL TRIAL DESIGN

4.1 Clinical Trial *Endpoints*

The final outcomes of the clinical trial to be determined from this study are

4.1.1 Primary result

- ✓ Difference in mean thermal sensation scale between topical application of menthol gel and placebo

4.1.2 Secondary result

- ✓ Difference in mean body temperature between topical application of menthol gel and placebo
- ✓ Difference in mean heart rate frequency between topical application of menthol gel and placebo
- ✓ Mean difference in highest heart rate frequency between topical application of menthol gel and placebo
- ✓ Differences in physical performance in vertical jumping (difference in mean jump height between topical application of menthol gel and placebo)

- ✓ Mean difference in physical intensity in terms of *Rating Perceived Exertion* (RPE) between topical application of menthol gel and placebo
- ✓ Difference in mean duration (time) of running between topical application of menthol gel and placebo
- ✓ Mean difference in perceived comfort between topical application of menthol gel and placebo
- ✓ Difference in proportion of skin irritation category on the applied area between topical application of menthol gel and placebo
- ✓ Knowing the security profile, both non-serious and serious in nature

4.2 Research Design

This was a randomized, *cross-over*, *double-blind* study at one site: Eminence Clinic, which compared the application of 4% Menthol gel versus placebo gel. Running activities were carried out at the Athletic Field of GOR Soemantri.

4.3 Description to avoid bias

4.3.1 Randomization to Test Drug and Placebo

A randomization list of Subjects will be generated by the Statistical Consultant. Application of Test Drug and Placebo will follow the *random number table*. Each Subject will receive the test drug following the random number table (M.G. Kendall and B. Babington random number table. Cambridge University. 1954). In the event of adverse events in the Subjects, at the request of the Research Team, the confidentiality of the use of the Test Drug and the Placebo can be disclosed.

4.3.2 Impersonation

The test drug and placebo are in the form of light blue gel.

The test drug and placebo packaging tubes to be used in this study will be covered by packaging stickers. The research team is not allowed to have access to the test drug and placebo. Subjects are also not allowed to have access to the test drug and placebo.

The Research Site Coordinator will apply the test drug to the dose card according to the dose indicated on the dose card according to randomization. And will give it to the subjects at the stopping posts (3 stopping posts). So that both the research team and subjects only receive dose cards that have been applied to the test drug or placebo according to randomization.

4.4 Description of the treatment and dosage and its completeness of the product under study

4.4.1 The test drug consists of:

- Test Drug

Light blue gel with the trademark Counterpain COOL® (License Number: POM QD. 111 709 501) containing the active substance Menthol 4%.

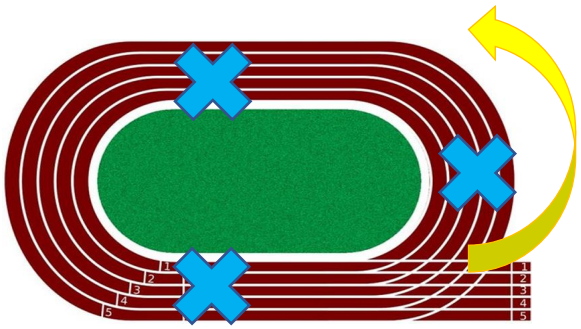
- Placebo
  Light blue gel where the active ingredient Menthol is replaced by purified water.

4.4.2 How and where to apply the gel

Each Subject will receive a *cross-over* application of 4% Menthol gel and placebo with the order of application *randomized* using a *random number table* and a minimum *wash out* period of 7 days± 1 day after the first application

The test drug, i.e. 4% Menthol gel or placebo, will be applied by rubbing on the neck area, the front side of the upper arm and the front side of the upper leg. The neck area was chosen because there is a carotid artery in the neck area, which is said to have an impact on changes in body temperature in the hypothalamus. In addition, the upper arm and upper leg areas were chosen because they are the extremity areas closest to the core of the body and perform a lot of movement while running. Some journals concluded that the application of cooling methods in the hand and thigh area is effective for cooling methods.

The application is adjusted to the Per (Mid) Cooling method, where the Subject will start applying the test drug while running on lap 7 (along kilometer 2.5 to 2.8).



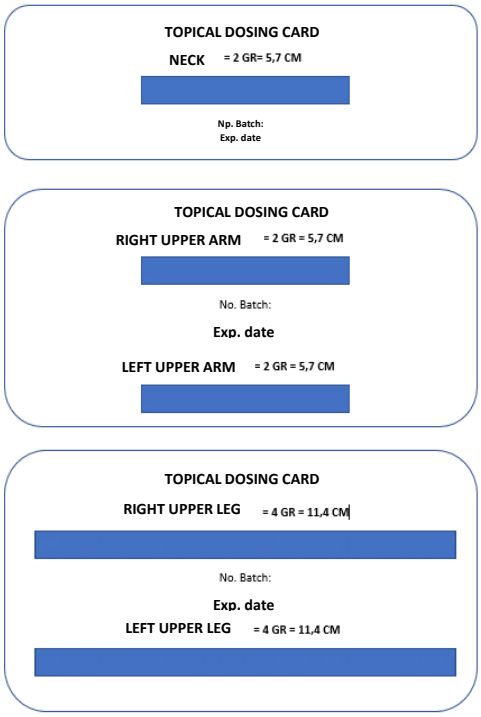
Description: ✖ = where dose cards are distributed by the Site Coordinator to subjects

dose of the test drug, 4% Menthol gel or placebo, was administered by following the dosage of topical drugs in general, as follows:[2]

- 2 grams (2.25 inches or 5.7cm) for the neck
- 4 grams (4.5 inches or 11.4cm) for each upper extremity (including upper arm or forearm) and lower extremity

The total dose given is not more than the maximum total dose limit of 32 grams in a day of use.

The test drug dose card consists of 3 dose cards consisting of dose cards for the neck, right and left upper arms, right and left upper limbs.



4.4.3 Tube packaging stickers

The packaging sticker will be used to cover the Test Drug and Placebo tubes. Only the Research Site Coordinator will have access to the test drug and placebo. The test drug and placebo will be stored at the research site in accordance with recommended temperature of 30°C. *A cooling box* will be provided to store the test drug and placebo at the research site if the air temperature exceeds 30°C.

For **CLINICAL TEST** only
Clinical trial drug (light blue gel)
Only to be applied on the dose card.
Batch No:
Exp date:

For **CLINICAL TEST** only
Placebo (light blue gel)
Only to be applied on the dose card.
Batch No:
Exp date:

4.5 Duration of Research

4.5.1 Research Schedule

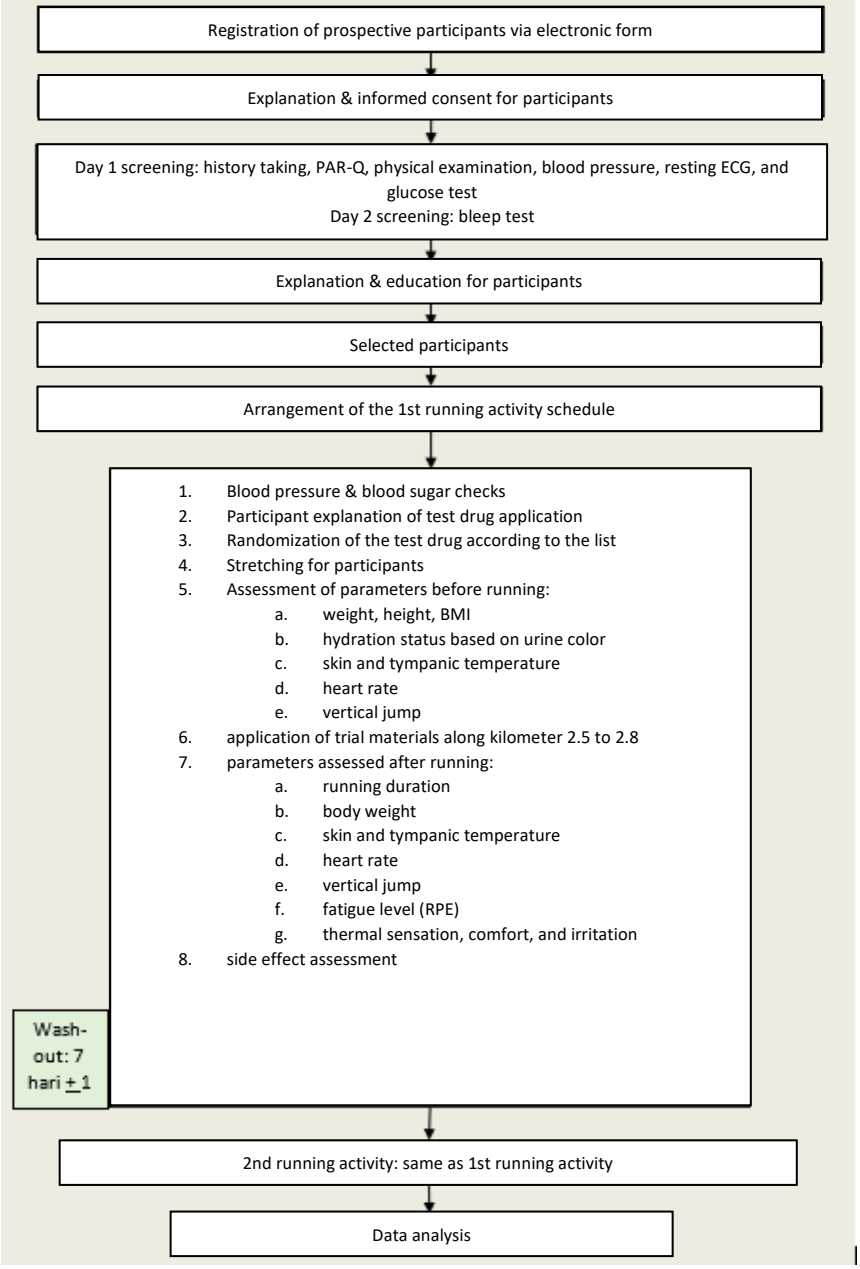
The study runs from May 2023 to December 2023. Each subject will require 5 visits with a wash-out period of 7 days±1 day. So, in total, each subject will need ±3 weeks to complete the study.

Running activities will be held at the Athletics Field, every Saturday and Sunday for two months. Only the three deepest tracks will be used for this activity. During the research activities, the Athletic Field will be closed to the public.

	Subject 1 Screening	**Subject 2 Screening**	**Intervention Period 1**	**Intervention Period 2**	**Research**
Visit	**1**	**2**	**3**	**4**	**5**
Day	**1**	**2**	**9 (Wash-out)**	**16**	**20**
Electronic Form	V				
Informed Consent Subject	V				
Anamnesis and PAR-Q Questionnaire	V				
Physical examination, blood pressure, blood sugar and resting ECG, Covid 19	V				
Bleep Test		V			
Intervention Period Preparation Education		V			
Blood Pressure Check Before Running			V	V	
Education on how to apply test products			V	V	
Weight and Height Check			V	V	
Hydration Status			V	V	
Heart Rate			V	V	
Skin and Tympanic			V	V	

Temperature					
Vertical Jump			V	V	
Test Drug Intervention			V	V	
Physical Checkup After Running			V	V	
Body Weight			V	V	
Skin and Tympanic Temperature			V	V	
Heart rate			V	V	
Vertical Jump			V	V	
RPE			V	V	
Running duration			V	V	
Thermal sensation, comfort and irritation			V	V	
Occurrence of Side Effects			V	V	
Finish					V

4.5.2 Research Flow



4.6 Description of Termination Rules

All studies were stopped or interrupted by the following procedures.

1. When an entire study is terminated or discontinued, the Sponsor immediately notifies all principal investigators involved in the study and the regulatory agency of that and the detailed reasons in writing.
2. When the Sponsor decides to terminate or discontinue the entire study and notifies the PI of the decision, the PI immediately notifies the institutional review board about it in writing and explains the details of the termination or discontinuation to the institutional review board.

3. When the principal investigators were notified of the discontinuation or termination of the entire study, they immediately informed the subjects who received the study treatment to that effect and took appropriate actions including switching to another therapy.

4.7 Accountability procedures for the product under study

The test drug and placebo will be stored at the research site in accordance with the recommended temperature of below 30°C. *A cooling box* will be provided to store the test drug and placebo at the research site if the air temperature exceeds 30°C.

4.8 Maintain random code

The study site coordinator has full access to the randomization and is responsible for the administration of test drugs in the field.

The research team did not have access to randomization and test drugs.

4.9 Data identification

Individuals interested in becoming Subjects will be required to fill out an electronic registration form, which asks for identity data (name, date of birth, address, education, occupation, ethnicity, and contact phone number).

The research site coordinator will assign a unique code number to each Subject. The unique code number will be recorded in the examination status of the Subject.

5 SUBJECT SELECTION AND TERMINATION

5.1 Inclusion Criteria:

- Adults, 18 - 45 years old
- Have a *personal best* 10-kilometer run time of under one hour (which will be confirmed during the screening of prospective Subjects through history taking) in the last 6 months.
- Doing running training at least 3 times/week for the past 1 year
- Have a level of heart-lung endurance or VO_2max that is at least included in the *average* criteria (known through examination: *Bleep test*)
- Meets Subject screening criteria by answering "No" to all questions on the *Physical Activity Readiness Questionnaire* (PAR-Q) questionnaire.
- Have normal resting ECG and normal GDS results on screening of prospective Subjects.
- At the time of the study, the body temperature was within the normal range

5.2 Exclusion Criteria:

- Pregnant and/or breastfeeding women
- Have had a musculoskeletal injury in the last three months and still have symptoms or complaints
- Are experiencing acute infectious disorders, such as gastrointestinal, respiratory infections
- During treatment for chronic diseases (e.g. high blood pressure or hypertension, diabetes or diabetes mellitus, heart disease)
- Have a history of hypersensitivity or allergy to menthol or skin-applied products (especially gel-based products)
- Has a history of cold allergy
- Have a positive COVID-19 test result at the time of screening.

5.3 Subject Termination Criteria

Criteria for Subjects who were unable to continue the study:

- The subject was not at the research site at the time of data collection.
- The subject decided not to continue participating in the study.
- Subjects had COVID-19 infection during the study period
- The subject had an acute injury or inflammation during the study period that made them unable to participate in the study according to the research team

6 SUBJECT TREATMENT

6.1 Treatment to be given

The test drug consists of:

- Test Drug
  Light blue gel with the trademark Counterpain COOL® (License Number: POM QD. 111 709 501) containing the active substance Menthol 4%.
- Placebo
  Light blue gel where the active ingredient Menthol is replaced by *purified water*.

6.2 Allowable and unallowable treatments

6.2.1 Allowed and disallowed medicines

Medicines that are allowed to be consumed are vitamins and minerals within reasonable limits. The drugs that are not allowed to be consumed are a list of drugs that are on the *World Anti-Doping Agency* (WADA) list such as:

- Drugs that belong to the Anabolic group
- Drugs that belong to the group of peptide hormones and growth hormones
- Drugs belonging to the metabolic hormone group

- Drugs that belong to the Beta agonist group
- Drugs that belong to the Diuretics group
- Drugs that belong to the Stimulant group
- Drugs that belong to the Narcotic group
- Glucocorticoid drugs

6.2.2 Medicines for first aid

In this study, Subjects are likely to experience several kinds of health problems due to the intervention provided, namely musculoskeletal injuries, wounds or *exertional heat illness* due to running activities, or skin health problems related to the experimental materials applied. To anticipate these various health problems, the Research Team provides various equipment and medicines that can be used to provide appropriate first aid.

No.	Equipment/Medicine	Total
1	Topical medication	
	a. Voltaren gel (anti-inflammatory)	1 tube 50 grams
	b. Kloretil *Spray*	2 cans
	c. Counterpain cream	2 tubes 120 grams
	d. Mofacort ointment (Mometasone furoate 0.1%)	1 tube
2	Wound care	
	a. Betadine antiseptic solution	1 bottle (30 mL)
	b. Sterile gauze	2 boxes
	c. 1-inch micropore	1 piece
	d. Hansaplast plaster	20 pieces
	e. Hansaplast Jumbo Plaster	10 pieces
3	Oral medication	
	a. Diclofenac sodium 25 mg	1 strip
	b. Eperisone HCl	1 strip
	c. Domperidone	1 strip
4	Injectable drugs	

	a. Epinefrine	2 ampoules
	b. Dexamethasone 5 mg/mL	2 ampoules
	c. Sodium chloride infusion solution 0.9%	1 colf (500 mL)
	d. Lactated Ringer's infusion solution	1 colf (500 mL)
5	Miscellaneous equipment	
	a. Oxycan	3 tubes
	b. Ice cubes	1 box/day
	c. Plastic bag with *zip*	1 pack
	d. *Plastic wrap*	1 piece
	e. *Elastic bandage* Tensocrepe 7.5 cm	1 piece
	f. *Elastic bandage* Tensocrepe 10 cm	1 piece
	g. *Elastic bandage* Tensocrepe 15 cm	1 piece
	h. 3 cc syringe	2 pieces
	i. *Alcohol swab*	1 box (100 pieces)
	j. Scissors	1 piece
	k. KN95 Mask	3 *boxes*
	l. *Gloves/handscoon*	1 *box*
	m. AED	1 unit

6.3 Procedures to monitor Subject compliance

The research site coordinator ensures that the Subjects follow the rules set out in this study. The research site coordinator will provide education to Subjects on H-1, research day and H+1 as follows:

a. Subject preparation education:
   - Adequate rest the night before participating in research activities, which is at least 8 hours of night rest
   - Breakfast is required, 2 hours prior to the running activity
   - Wear appropriate sports shoes
   - Avoid drinking caffeine-containing beverages such as coffee, tea, cola, chocolate, and do not consume alcohol before the study.

- Remind the Subjects about the drugs they can and cannot take during the study period.

b. Education on the day of intervention:
   - Stretching according to the video shown
   - See how the test drug is applied through the video shown
   - Explaining how to fill in the analog visual score: thermal sensation and comfort acceptance.
   - Explain reporting if there are complaints or symptoms during the study time, you can immediately report them to the research team.

c. Education on the day after the intervention:
   - If there are complaints or symptoms during the study time, you can immediately report to the research team.

7. FINAL OUTCOME EFFICACY ASSESSMENT

7.1 Specification of result parameters

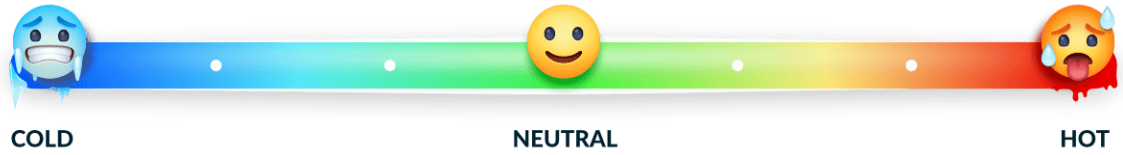
7.1.1 Primary result parameters

Thermal Sensation Check of the Subject

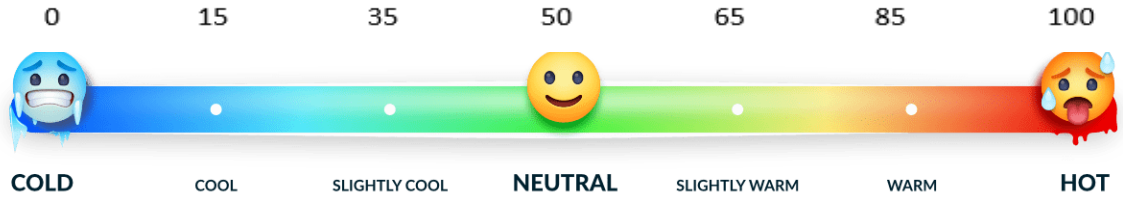
Education on how to fill out the thermal sensation visual analog score form will be given to each research subject on the intervention day before the running activity is carried out.
Thermal sensation is the ability to distinguish temperature differences.
Examination Thermal sensation on the skin will be measured using a visual analog scale.
Subjects were asked to provide an assessment of thermal sensation according to the translation of thermal sensation that has been validated by ISO 10551:

Language	Verbal anchors of sensation scale						
English	Cold	Cool	Slightly cool	Neutral	Slightly warm	Warm	Hot
Indonesian	Dingin	Sejuk	Agak sejuk	Tidak hangat maupun sejuk	Agak hangat	Hangat	Panas

In this study, it will use a thermal sensation examination with reference to the *American Society of Heating Refrigeration and Air conditioning Engineers (ASHRAE) standard 55-2004.* Visual Analogue Scale ASHRAE refers to 7 scale score assessment namely "cold", "cool", "slightly cool", "neutral", "slightly warm", "warm" and "hot".
Subjects will rate the visual analog scale as follows:

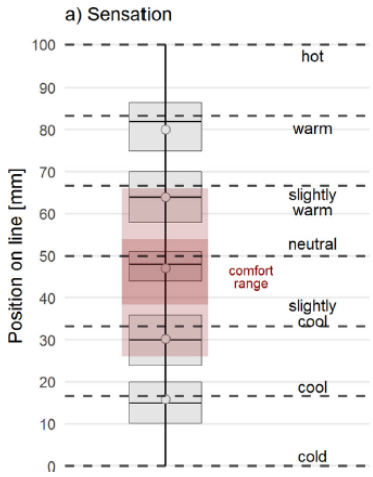


After filling in the visual analog scale, the assessment of the visual analog scale score conducted by the researcher is as follows below:



Reference:M. Schweiker, M. André and F. Al-Atrash et al. / Energy & Buildings 211 (2020) 109761

The assessment of the Thermal Sensation score corresponds to the scale in millimeters (mm) as follows:



7.1.2 Secondary result parameters

a. Body Temperature

Measurement of skin and tympanic temperature in accordance with the procedure is carried out twice during each running activity. The first measurement was taken when the Subject was standing in the starting line area. The second measurement was taken immediately after the Subject finished running

Skin temperature measurements will be taken in 5 areas: calf, thigh, abdomen, upper arm, lower neck (close to the chest).

b. Heart Rate

Heart rate (HR) was recorded using a Polar Heart Rate Monitor before the start of the exercise protocol until the completion of the exercise. Upon completion of the exercise, the equipment was immediately removed. From the results of the heart rate monitoring, the following two things were recorded:

- Average heart rate during activity
- Highest heart rate during exertion

c. Physical performance ability / *Vertical Jump*

The *vertical jump* examination is carried out after the subject warms up in the form of *jogging* or running 1 lap and doing static stretching according to the guidelines of the Research Team. *Vertical jump* will also be done after the subject completes a 5 km running session.

- The *vertical jump* height is the difference between two marked points on the wall. All Subjects jumped three times, with a minimum interval of 45 seconds between jumps. The data used was the highest *vertical jump* (cm).

d. Physical Exercise Intensity Assessment using *Rating Perceived Exertion* (RPE)

Rating of Perceived Exertion (RPE) is a scale created by Gunnar Borg's in 1982, and aims to measure and determine the intensity or effort expended during physical activity, based on a person's subjective perception that is quantified. RPE is highly correlated with heart rate, maximal oxygen uptake, and lactic acid levels during physical activity.

e. Running Duration

The researcher calculated the amount of time taken by the Subject to complete a 5-kilometer run (in minutes).

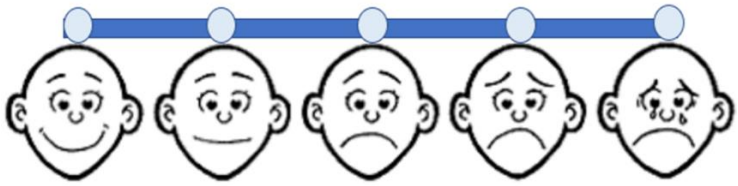
f. Comfort perception (acceptance) assessment

Education on how to fill out the thermal sensation visual analog score form will be given to each research subject on the intervention day before the running activity is carried out.

BS EN ISO 7730 defines thermal comfort as '...a state of mind that expresses satisfaction with the thermal environment.'

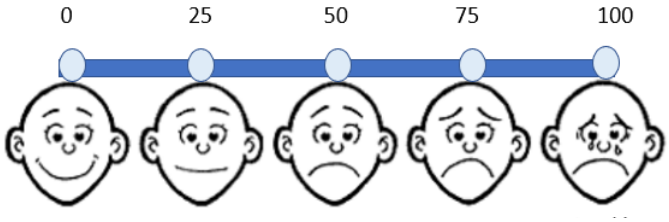
According to the Big Indonesian Dictionary (KBBI), comfort is a state of comfort, freshness, or coolness.

ISO 10551-2019 measures the perception (acceptance) of comfort measured using the following scale: "Comfortable", "Slightly uncomfortable", "Uncomfortable", "Very uncomfortable", "Extremely uncomfortable".



Comfortable Uncomfortable Extremely uncomfortable

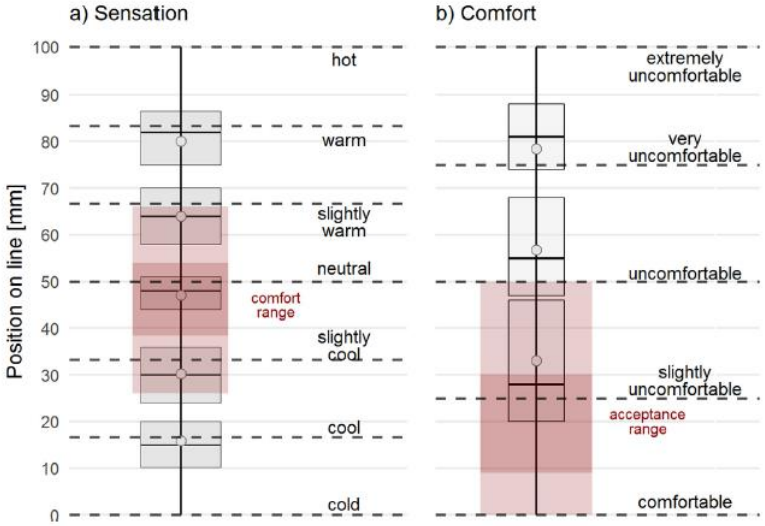
After filling in the visual analog scale, the assessment of the visual analog scale score conducted by the researcher is as follows below:



Comfortable Uncomfortable Extremely uncomfortable

Reference:M. Schweiker, M. André and F. Al-Atrash et al. / Energy & Buildings 211 (2020) 109761

The assessment of the comfort perception score corresponds to a scale in millimeters (mm) as follows:



g. Examination of irritation by the researcher is when the subject has finished running activities (finish), using the International Contact Dermatitis Research Group (ICDRG) score as follows:

Symbol	Morphology	Assessment
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Note: Table of European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice.2015

7.2 Safety assessment

7.2.1 Definition of AE

In this study, *adverse events* (AEs) refer to all unwanted medical events in Subjects administered the medicinal product. AEs can be unwanted symptoms or signs (including abnormal laboratory findings), or transient illness, whether or not related to the (investigational) medicinal product.

7.2.2 AE Observation

The researcher asks the Subject about AEs and checks for abnormal changes on physical examination. When an AE occurred during the study (i.e. within the observation and treatment period), the Investigator entered the items indicated in the "Evaluation Method and Criteria for AEs and other items necessary for the assessment of the safety of the study drug in the case report form and followed up the AE until it recovered.

7.2.3 Evaluation Method and AE Criteria

a. AE name

Names of symptoms, findings, and diseases or names of laboratory or other tests are identified.

b. Start Date

The day on which the AE was observed was determined. The day of onset is defined as follows. When symptoms or signs are observed and the cause is subsequently identified: The day on which the symptom or sign was first observed.

c. Severity

The severity of AEs is differentiated based on the following 3-point scale:

- Mild: An event that is easily tolerated by the Subject, causes minimal discomfort and does not interfere with daily activities.
- Moderate: An event that is unpleasant enough to interfere with normal daily activities.
- Severe: An event that prevents normal daily activities.

d. Seriousness

The seriousness of AE can be divided into:

- Seriously
- Not Serious

e. Measures Taken for Study Medicine

Among the 3 action steps taken for the following study drugs, the one that was applied was included in the case report form.

- None (continued/treatment completed)
- Dose interruption
- Discontinued

f. AE Maintenance

AE treatment is investigated until the end of AE treatment. The names of all drugs used or all therapies used will be investigated and included in the case report form. However, this does not apply when follow-up examination is stopped based on sufficient medical reasons or when follow-up becomes impossible for reasons including death not caused by the AE or transfer to another clinic or hospital

In case of skin irritation such as allergic contact dermatitis, the first treatment is to immediately clean the area with clean cold water, compress with betadine using sterile gauze, after that provide treatment according to the symptoms, for example topical calamine can be given for itching, topical corticosteroid preparations to relieve inflammation and antibiotics if there is a possibility of bacterial infection. The Subject will then be referred to a Referral Hospital for further treatment by a competent Doctor. (see list of first aid medicines point 6.2.2).

Injuries related to *heat-related illness* will be treated according to the symptoms and if necessary, will be referred to the Referral Hospital for further treatment.

g. AE Trip Results

Classified into 4 categories as follows:

- Recover
- Improving
- Unchanged

- Worsening

h. Result Date

Outcome day is defined as the last day on which the Investigator can directly confirm or classify the outcome. Follow-up investigations are conducted until the event recovers. However, when it is deemed unnecessary to follow up the complaint until it recovers, the specified day need not be considered as the outcome day. When the outcome day cannot be accurately determined due to reasons including missed site visits, the day on which the outcome is confirmed or assessed over the phone or by mail is considered the outcome day.

i. Causal Relationship with Study Drugs and Definition of ADRs

Causal relationships with study drugs are classified into 4 categories as follows:

- Definitely
- Very likely
- May
- Not related

7.2.4 Serious side effects

7.2.4.1 Definition of a Serious AE

A serious AE among AEs is defined as follows.

1. Fatal (death)
2. Life-threatening (may cause death)
3. Requires hospitalization or extended hospitalization for treatment
4. Causes permanent or actual disability or dysfunction
5. Causes congenital abnormalities
6. Other significant medical events, i.e., significant events that expose the patient to risk or require treatment to avoid the above outcomes (1) to (5) even if they are not life-threatening or cause death or immediate hospitalization.

7.2.4.2 Response to Serious AE Alert

1. When a serious AE occurs, the PI immediately notifies the Sponsor (monitor) verbally or by phone, email or fax and reports details in writing at a later date. In these cases, the principal investigator identifies unexpected ADRs (the characteristics and severity of which correspond to the information in the investigator brochure) among the serious AEs to be reported.
2. When the Sponsor and institutional review board requested additional information (autopsy reports, terminal stage medical records, and other necessary information) regarding the reported serious AEs, the principal investigator provided this information.
3. The sponsor promptly notified all principal investigators involved in the study of all events that should be reported to BPOM RI immediately.

7.2.4.3 Handling of Serious AE Events

a. Anaphylactic Shock

1. Position the patient lying supine (pregnant patient on the left side) with the legs elevated.
2. Check *Airway, Breathing, Circulation, Disability, Exposure* (whether history of severe allergic reaction, rapid onset, *respiratory compromise* or hypotension, or organ failure, with skin changes).
3. If there is an *exposure*, identify and stop contact with the allergen.
4. Give 0_2 8 L/min. Place an intravenous line.
5. Give 0.3-0.5 ml intramuscular injection of adrenaline/epinephrine 1:1,000 IM in the lateral thigh.
6. Repeat 10-15 minutes if there is no clinical improvement. Maximum of 3 doses.
7. If there is hypotension or tachycardia, fluid 1 liter
8. Diphenhydramine is given to treat additional symptoms such as pruritus, erythema, and urticaria at a dose of 1.25 mg/kg, maximum 50 mg IM. Give it once. Given only after epinephrine has been administered.

b. Hypovolemic Shock

The initial management of patients with no hemorrhagic hypovolemic shock is:

- determining fluid deficit
- Overcome shock by giving crystalloid fluid (RL fluid or NaCl 0.9%) 20 mL/kgBB in 30 - 60 minutes, can be repeated.
- The remainder of the fluid deficit can be given in percentages: 50% in the first 8 hours and 50% in the following 16 hours.
- Clinical signs of hypovolemia have been resolved / hydration, if urine production: 0.5 - 1 mL / kg / hour

Infusion Fluid (Isotonic Balanced Full Electrolyte Solutions)

Indications for administration in all cases of shock, when cardiac preload is reduced due to reduced intravascular volume or obstruction. The mechanism of action is by replacing fluid loss due to electrolyte imbalance or volume shift, increasing stroke volume by increasing *cardiac preload*.

Side effects can occur *volume overload, pulmonary edema , peripheral edema*. The initial dose of 10-20 mL/kg IV can be given continuously depending on the effect and patient response.

Administration of Vasoconstrictors, Positive Inotropic Agents, and Vasodilators

- Epinephrine

Indications for epinephrine administration are in all types of shock, when the use of other catecholamines fails to achieve the desired state of vasoconstriction and increase inotropic: cardiopulmonary resuscitation, anaphylactic shock. The mechanism of action of epinephrine causes constriction through *α1-receptor-mediated vasoconstriction* and *β1-receptor-mediated positive inotropic* and *β2-receptor-mediated bronchodilation*.

Side effects that may occur are *myocardial ischemia, stress cardiomyopathy, tachyarrhythmias*, oliguria/anuria.

The dose of epinephrine is 0.3-0.6 mg IM, can be given continuously based on effect and need: 0.05 to 1.0 (up to a maximum dose of 5.0) µg/kg/min IV administration during cardiopulmonary resuscitation: 1 mg IV. every 3-5 minutes.

- Dobutamine

Indications for the administration of dobutamine in all types of shock with ventricular pump function insufficiency, the mechanism of action of dobutamine is mainly β1-receptor mediated positive inotropic effect, side effects that can occur are increased heart rate ≥ 30 / min, increased blood pressure ≥ 50 mmHg, headache, cardiac arrhythmias, the possibility of a decrease in blood pressure caused by *β2-receptor-mediated vasodilation*.

The dose of dobutamine can be given continuously depending on the effect and needs of each patient i.e.: 2.5 to 5 (with a maximum dose of 10) µg/kg per min IV.

- Norepinephrine

Indications norepinephrine is administered in all types of shock with decreased peripheral resistance. The mechanism of action is mainly *α1-receptor mediated vasoconstriction*, *(low) positive inotropic effects*. Possible side effects are peripheral ischemia, increased blood pressure, *reflex bradycardia, and cardiac arrhythmias*.

Continuous doses are given depending on effect and need i.e.: 0.1-1.0 µg/kg/min IV. bolus administration: 5-10 µg IV

c. Neurogenic Shock

The management of neurogenic shock includes three aspects:

- Hemodynamic stabilization with target means arterial pressure (MAP) and cerebral perfusion pressure of >85-90 mmHg and >70 mmHg within 7 days.

Hypotension needs to be treated immediately with target mean arterial pressure (MAP) and cerebral perfusion pressure of >85-90 mmHg and >70 mmHg within 7 days. In neurogenic shock with traumatic etiology, hypotension may result from hemorrhagic shock rather than neurogenic shock. For this reason, hypotension treatment needs to begin with a fluid challenge or administration of crystalloid fluids (lactated ringer or NaCl 0.9%) or colloids up to a maximum of 2 L. Mannitol administration needs to be avoided in patients with suspicion of traumatic brain injury or spinal cord injury.

Second-line therapy for the management of hypotension in neurogenic shock is vasopressor and inotropic agents. Norepinephrine is preferred as phenylephrine may cause reflex bradycardia. Therefore, norepinephrine is preferred.

Insert a urine catheter to monitor urine output and to decompress the neurogenic bladder. Urine output should be maintained at >0.5-1 ml/kgBB/hour.

Patients should be subjected to continuous cardiac monitoring including ECG, blood pressure, and oxygen saturation monitoring. Hospitalize the patient in the ICU.

- Prevention of further spinal cord damage

To prevent further spinal cord damage, the following steps can be taken:

- Oxygenation and/or ventilator use
- Stabilization of cervical vertebrae
- Surgery for decompression and shock repair
- Corticosteroid administration has shown potential benefit in animal studies but has not been shown to be beneficial in clinical trials and may increase the risk of complications.

- Management of bradycardia or another arrhythmia

Management of bradycardia can be done by administering atropine, glycopyrrolate, or isoproterenol. If the bradycardia does not respond to the drugs given, methylxanthines such as theophylline and aminophylline or propantheline can be given. In addition to bradycardia, another arrhythmia such as AV block, or atrial fibrillation may also occur. Treat according to the principles of handling each type of arrhythmia.

d. Cardiogenic Shock

Cardiogenic shock can be caused by acute coronary syndrome and its mechanical complications (such as chordae rupture, interventricular septal (IVS) rupture, and ventricular wall rupture), heart valve abnormalities, and severe heart failure in other myocardial disorders. It is known that there is impaired consciousness ranging from mild to severe conditions, decreased diuresis, may be accompanied by cold sweat, weak pulse, there are signs of hypoperfusion such as (cold extremity skin touch, tachycardia, weak pulse, hypotension, reduced bowel noise, oliguria), there are signs of increased preload such as increased JVP or wet rales at basal, *wet and cold* hemodynamic profile.

Acute phase management in the ED or ICVCU

- Total bedrest
- Perform cardiac resuscitation in case of cardiac arrest
- Sedation with midazolam, propofol or morphine
- Oxygen support (NRM or CPAP, intubation in case of respiratory failure)
- IVFD insertion

- If there is a rhythm disturbance such as tachycardia/bradyarrhythmia, treat it immediately with anti-arhythmic preparations or pacemaker, over drive or cardioversion.
- Invasive or non-invasive monitoring to determine the status of preload, SVR and cardiac output (CO).
- If preload is low, a fluid challenge of 1-4 cc/bodyweight in kg/10 minutes is given until preload is confirmed.
- If CO is low with high SVR but MAP is still <70 mmHg, inotropic vasodilator (dobutamine) or inodilator (milrinone) preparations should be given. IABP placement should be recommended in shock patients with acute coronary syndrome.
- If CO is high with low SVR, then vasopressor preparations such as noradrenaline or adrenaline or dopamine are given.
- Low dose dopamine can be given in oliguria.
- In refractory cardiogenic shock consider insertion of IABP, ECMO or LVAD as definitive *bridging* therapy.
- Definitive therapy such as PCI, valve replacement surgery, BMV (in MS), urgent CABG should be performed immediately, or heart transplantation if possible.
- All cardiogenic shock patients should be admitted to the CVCU.

8 STATISTICS

8.1 Statistical Methods

Univariate analysis was conducted to see the description of each dependent and independent variable. For variables that are numerical variables, a distribution test will be conducted. If the variable has a normal distribution, the data will be presented in the form of *mean* and standard deviation. Meanwhile, if the variable has an abnormal distribution, the data will be presented in the form of median and minimum and maximum values. Variables that are nominal or ordinal variables will be presented in the form of a frequency distribution for each category.

Bivariate analysis will be conducted according to the following specific objectives:

1. To analyze whether there is a difference in variables that are numerical variables, a *paired T-test* is conducted. If the paired T-test does not meet the requirements, the Wilcoxon test will be conducted.
2. For variables that are nominal or ordinal variables, the Chi-square test is performed. If the Chi-square test is not eligible, Fisher's exact test will be performed.

8.2 Number of subjects

8.2.1 Subject calculation (thermal sensation)

The study design was cross over, with the aim of seeing the thermal sensation between the groups given menthol gel and placebo gel.

Where for standard deviation, **the largest** standard deviation of various thermal sensation data due to the use of menthol in physical exercise is selected.

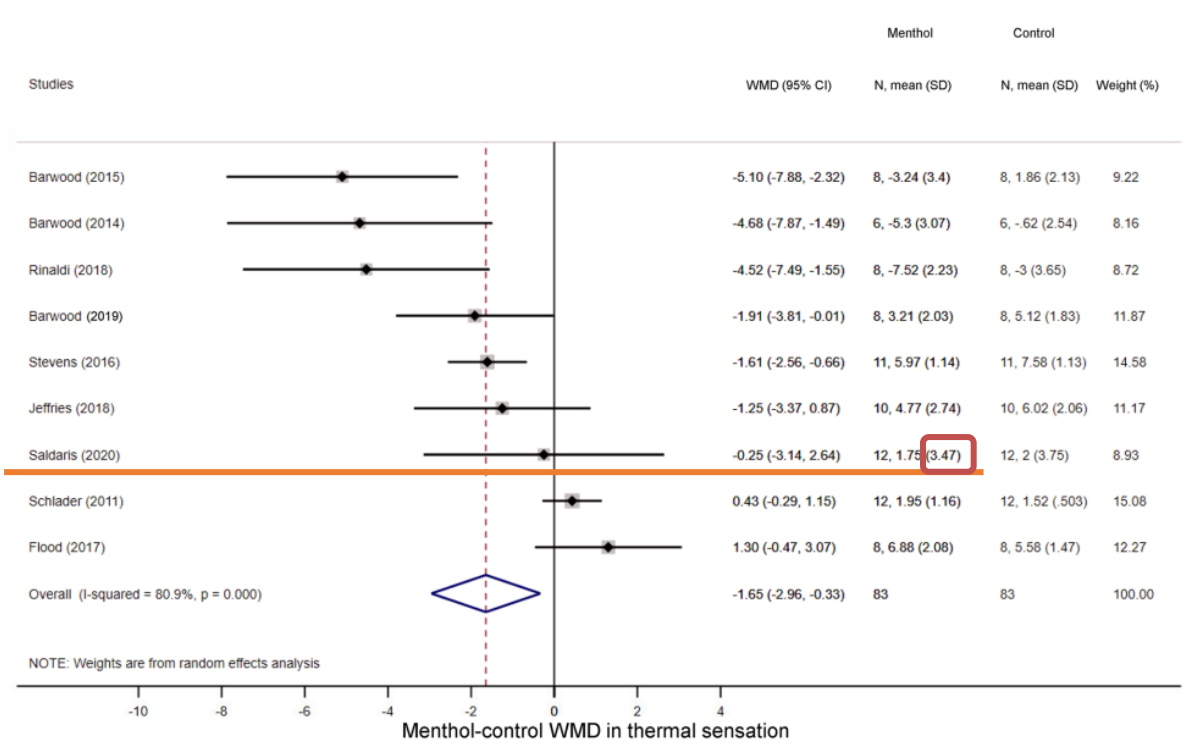


Figure 2. Forest plot of the weighted mean differences (WMDs) showing the effect of menthol on thermal sensation during exercise. Here, and in Figs. 3, 4, 5, 6, 7, and 8, black circles represent the WMD for each study,

The formula is as follows:

$$N = \frac{(Z_\alpha + Z_\beta)^2 \, x \, SD_d^2}{(x_1 - x_2)^2}$$

- N = number of subjects
- $\alpha = 0.05$, then $Z_\alpha = 1.96$
- Research *power* = 0.9, then $Z_\beta = 1.282$
- SDd = Standard deviation of the mean difference in thermal sensation in both treatment groups = 3.47
- X1-X2= difference in thermal sensation between the two treatment groups that is considered clinically meaningful = 3 (based on the clinical judgment of the

researchers, where in general, in the medical world, a difference of more than 15% is considered a meaningful difference [for example in terms of differences in left and right-side muscle strength]).

$$N = \frac{(1{,}96+1{,}282)^2 \times 3{,}47^2}{3^2}$$

$$N = 14.06 \rightarrow 15$$

By calculating the dropout calculation, assuming the dropout is 10%, using the formula:

$$N' = \frac{N}{1-f}$$

Therefore, the number of subjects is 16.67 = 17 subjects per group.

8.2.2 Subject calculation (temperature change)

The study design was cross over, with the aim of seeing the temperature difference between the groups given menthol gel and placebo gel.

Where for the standard deviation, the largest standard deviation is selected from various data on temperature changes due to the use of menthol in physical exercise.

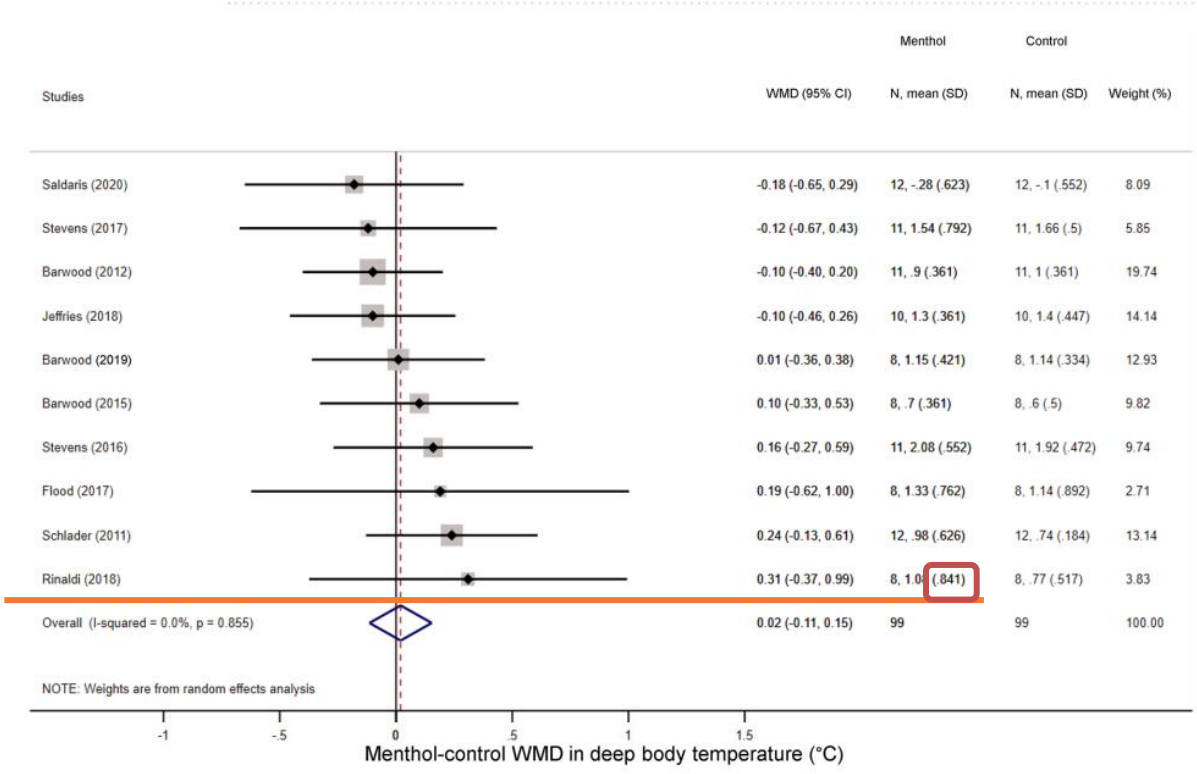


Figure 6. Forest plot of the weighted mean of differences (WMDs) for deep body temperature showing the effect of menthol during exercise.

The formula is as follows:

$$N = \frac{(Z_\alpha + Z_\beta)^2 \, x \, SD_d^2}{(x_1 - x_2)^2}$$

- N = number of subjects
- α = 0.05, then Z_α = 1.96
- Research *power* = 0.9, then Z_β = 1.282
- SDd = Standard deviation of the mean difference in body temperature changes in the two treatment groups = 0.840C
- X1-X2= difference in body temperature reduction between the two treatment groups that is considered clinically meaningful = 0.5^0C (based on the clinical judgment of the researchers)

N = $\frac{(1,96+1,282)^2 \text{ x } 0,841^2}{0,5^2}$

N = 29.66→ 30

By calculating the dropout calculation, assuming the dropout is 10%, using the formula:

$$N' = \frac{N}{1 - f}$$

Therefore, the number of subjects is 33.33 = 34 subjects per group.

8.2.3 Conclusion Number of subjects

Based on the calculation of the number of subjects above, the minimum number of subjects recruited in accordance with the primary objective is 17 subjects.

In order to be able to analyze all objectives, both primary and secondary, and following the existing randomization method, the number of subjects to be recruited in this study was **36 subjects.**

8.3 Criteria for stopping a clinical trial

The sponsor immediately discusses discontinuation or termination of the study with the medical expert when the following criteria are met and continuation of the study at all study sites is deemed difficult or meaningless.

1. When an "unexpected" serious AE (illness, impairment, death) occurs.
2. When information indicating that the "expected" occurrence of significant AEs including the number of incidents, frequency, and conditions of occurrence cannot be predicted based on the investigator's brochure is obtained.
3. When information indicating that trends in the occurrence of ADRs including the number of incidents, frequency, and conditions for occurrence are changing markedly for the worse is obtained.

4. When information is obtained that indicates or does not indicate the superiority of the test drug over the comparator
5. When other information that affects the continuation of the research is obtained.

9 . DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1 Direct Access to Source Documents

Principal investigators accept monitoring and auditing by the Sponsor and inspection by institutional review boards and regulatory bodies and make all study-related records including source documents available for direct access.

9.2 Direct Access Method

Each study site and Sponsor determined the method of direct access through discussion.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor responsibly conducts quality assurance based on standard operating procedures and maintains a quality control system to ensure that research is conducted and data are generated, recorded, and reported in accordance with the protocol, pharmaceutical affairs laws, and GCP.

10.1 Study Quality Control

The Sponsor implements quality control at each step of data handling to ensure the reliability of all study-related data and appropriate processing. Monitors assigned by the Sponsor conduct monitoring (including direct access to study-related records such as source documents) in accordance with standard operating procedures and confirm that research is being conducted appropriately at the study site in accordance with protocols, standard operating procedures, and GCP. The monitor, the person in charge of the quality control system, the person in charge of data management, and the person in charge of statistical analysis perform quality control at each step of data handling according to standard operating procedures established by the Sponsor.

10.2 Study Quality Assurance

The Sponsor assures the quality of research by establishing an audit department that is independent of the department conducting the research. To ensure the quality of the research, personnel responsible for audits conduct audits at appropriate times at the Sponsor as well as at research sites and other facilities involved in the research as necessary, in accordance with the Sponsor's standard operating procedures.

10.3 Study Completion

The study completion day for each Subject was defined as "the day on which observations of all items specified in the protocol were completed or the termination day for the Subject"

and the study completion day for each study site as "the last day of research data collection at the study site in question." Once the study and observations specified in the protocol were completed for the last subject at the study site in question, the principal investigator immediately notified the institutional review board and sponsor of the completion of the study in writing and reported an outline of the study results based on the prepared report.

11 ETHIC

11.1 Study Overview

The study was reviewed by institutional review boards selected by each study site, whether or not the implementation was appropriate from the perspective of ethical, scientific and medical adequacy.

11.2 Overview of Continuing Studies

The adequacy of continued implementation of this study at specific study sites is reviewed once a year or more frequently, or in the following cases.

1. When the Sponsor notifies the PI of a serious and unexpected ADR or other event
2. When PIs report serious AEs or other events
3. When the PI reports revised consent forms and other written information to the Subjects
4. When the principal investigator submits an overview of the current status of the research for review regarding the continuation of the research
5. Other matters that the principal investigator felt needed to be reviewed regarding the continuation of her research

The PI requests the opinion of the institutional review board on the adequacy of continuing the research at the research site in question.

11.3 Matters Relating to the Protection of Privacy and Personal Information of Subjects

To protect the privacy and personal information of the Subject, the Subject is identified by the Subject ID.

In the preparation and handling of case report forms and monitoring, auditing, and other tasks performed by the Sponsor, as well as when study results are published, attention is paid to the protection of the privacy and personal information of subjects.

12 DATA HANDLING AND DOCUMENT STORAGE

12.1 Principal Investigator

Essential documents should be retained until at least 2 years after the last approval of the marketing application related to the test drug and until no marketing application is pending or under consideration or at least 2 years have elapsed since the formal cessation of clinical development of the investigational product. However, these documents should be retained

for a longer period, if required by applicable regulatory requirements or by agreement with the Sponsor.

12.2 Sponsor

1. Sponsor-specific critical documents should be retained until at least 2 years after the last approval of a marketing application in the ICH region and until there are no pending or planned marketing applications in the ICH region or at least 2 years have passed since the formal cessation of clinical development of the investigational product. These documents should be retained for longer periods but only if required by applicable regulatory requirements or if required by the Sponsor.
2. In the event that retention of documents that should be retained by the principal investigator or assessment body becomes unnecessary, the Sponsor notifies the assessment body through the Investigator.

13 FINANCE AND INSURANCE

13.1 Finance

The sponsor paid for this research based on the contract with each research site.

13.2 Insurance

The sponsor takes necessary measures including purchasing insurance policies to compensate for the treatment of subject health hazards caused by the research and other losses.

14 PUBLICATION POLICY

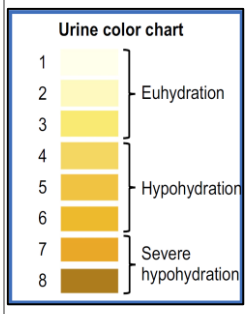
This study data is owned by the Research team and the Sponsor. In this case the Sponsor is free to use the information obtained in this study for purposes including applications for marketing approval related to the test drug and also for marketing related to the test drug.

15 OPERATIONAL DEFINITIONS

Variables	Operational Definition	Measurement tool	How to measure	Measurement unit	Variable scale
Gender	Determination of the gender identity recorded on the KTP (Identity Card) of each research subject	Data on ID card	Check the suitability of the ID card	Male and female	Nominal
Age	The biological age of the subject calculated from the date of birth in units of years	Data on ID card	Check suitability on ID card	Year	Numerical
Body weight	Subject's weight measured in minimal	Body scales	The subject stands upright on the scale	Unit kilogram	Numerical

	clothing		without using footwear, the results on the scale are seen		
Height	Height of the subject measured from the soles of the feet to the tip of the head in a vertical plane	Stadiometer	The subject stands upright barefoot with the back of the head, upper back, buttocks and heels against the wall. The gaze is forward and the chin is parallel to the floor. Then, the stadiometer plate was placed directly above the Subject's head.	Unit cm	Numeric al
Blood Pressure	Examination with a special device called a sphygmomanometer, which aims to measure the pressure in the arterial blood vessels when the heart beats.	Sphygmoma nometer	The subject is seated and relaxed, arm at heart level, cuff is placed, and blood pressure is calculated.	JNC VIII Scale Normal BP Systolic <120 mmHg; Diastolic <80 mmHg Prehypertension: Systolic 120 - 139 mmHg ; Diastolic 80 - 89 mmHg Hypertension gr.1: Systolic 140 -159 mmHg ; Diastolic 90 - 99 mmHg Hypertension gr.2: Systolic > 160 mmHg ; Diastolic > 100 mmHg	Ordinal
Instantaneou s Blood Sugar	a blood glucose test that can be done at any time without the need to fast first. used as a screening for diabetes, also done routinely to monitor blood glucose levels.	Timed Blood Sugar Strips and Examiner	Wash your hands thoroughly Place the *lancet* needle into the *lancing* device. Insert the test strip into the glucose meter. Wipe your fingertips with an alcohol-treated cotton swab. Prick your fingertip with a *lancet* to allow blood to be drawn. Place a drop of blood on the drip	blood sugar level < 200 mg/dL and without classic symptoms of diabetes mellitus through history taking	Numeric al

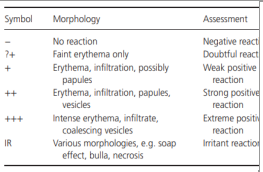
			strip and wait for the results. Usually, a number indicating your blood sugar level will appear within a few seconds on the meter screen.		
Electrocardiography (ECG)	Tests to evaluate heart health, including knowing and measuring whether a person's heart rate is normal or not.	An electrical impulse detection machine called an electrocardiograph	During the examination, electrodes are attached to the chest, arms and legs. There are usually 10 or 12 electrodes, made of plastic, and small in size. Each electrode cable is connected to an ECG machine to record the heart's electrical activity.	**P wave** Normal values: Width ≤ 0.12 seconds High ≤ 0.3 mV Always (+) in lead II Always (-) in aVR leads **PR Interval** Measured from the beginning of the P wave to the beginning of the QRS wave. Normal values range from 0.12-0.20 seconds. **QRS wave (QRS complex)** Normal values: width 0.04 - 0.12 seconds, height depending on the lead. Q wave: first negative deflection of QRS wave Normal values: width < 0.04 s, depth < 1/3 of R wave. If depth > 1/3 of R wave height, *pathological Q.* The R wave is the first positive deflection of the QRS wave. Generally, in leads aVR, V1 and V2, the S wave is deeper, while in leads V4, V5 and V6 it disappears or decreases in depth.	Category

				<u>T wave</u> Represents the ventricular repolarization process. Generally positive T wave, in almost all leads except in aVR **<u>U-wave</u>** Is a positive deflection after the T wave and before the next P wave.	
Body mass index	Indicators for determining nutritional status	Body scales and stadiometer	The ratio of body weight (in kilograms / kg) to the square of height (in square meters / m^2)	< 18.5 kg/m^2 : underweight 18.5-22.9 kg/m^2 : normal ≥ 23 kg/m^2: overweight ≥ 25 kg/m^2 : obese	Ordinal
Hydration status before running	An overview of SP's water in and out balance before the running intervention	Urine color degree table	Subjects were asked to collect urine samples in the urine pot provided. Then the subject's urine color is matched with the urine color table 	1-3 : good hydration 4-6 : less well hydrated 7-8 : fluid deficiency. *This urine color is in accordance with PURI, Practical Manual for Meeting Fluid Requirements in Physical Training. PDSKO. First Edition. 2014	Ordinal
Hydration status after running	An overview of SP's water in and out balance after the running intervention	Body scales	The percentage of SP body weight loss was calculated using the formula: $\frac{(BB\ sebelum\ berlari - BB\ setelah\ b}{BB\ sebelum\ berlari} \times 100\%$	≤ 2% : not dehydrated > 2% : dehydration[31]	Category
Vertical jump	One of the fitness parameters to measure leg *explosive*	Talcum powder	The subject places their powdered finger against the wall while	cm	Numeric al

	power is by measuring jump height.		standing upright facing sideways with the wall on their right side, then the right shoulder is maximally induced with the right arm and hand in a maximal extension position; the subject will mark the highest point that can be reached with the finger in the standing position. After that, the subject will be asked to jump as high as possible. At the highest point of the jump, the subject should extend the right hand to the wall to mark the maximum height of the jump with a powdered finger. The *vertical jump* height is the difference between two points marked on the wall. All subjects jumped three times, with a minimum interval of 45 seconds between jumps. The data used was the highest *vertical jump* data.		
WBGT *Temperature* (*Wet Bulb Globe Temperature*)	A measurement of *heat stress* by direct sunlight, which takes into account: temperature, humidity, wind speed, sun angle, and clouds (solar radiation).	WBGT	Turn the power on/off to the ON position. Select the unit of measurement. Select outdoor/indoor. Take temperature measurements on the measuring target (place).	<18°C : safe 18-24 °C : alert 24-28 °C : more alert 28-30 °C : dangerous >30 °C: extremely dangerous	Interval

			Record the measurement results.		
Heart-lung endurance level	The level of cardiopulmonary fitness as measured by the calculation of VO_2max	*Bleep Test*	Subjects were asked to run from one end or *markers cones* to the other end or *markers cones* 20 meters away by following the rhythm of the "beep" sound from the recording tape. The rhythm of this "beep" sound will become faster over time. If the subject failed to reach the *markers cones* before the "beep" sound was heard twice in a row, the subject was declared to have completed the test, and the number of laps was taken from the last lap that could reach the line. VO_2max values were determined based on the *Multistage Fitness Test (Bleep Test)* prediction table.	VO_2max category: very poor, poor, fair, good, excellent	Ordinal
Body temperature	The hot and cold state of the body measured by using a thermometer	Thermometer	Pull the top of the earlobe up and back. Gently insert the tip of the thermometer into the ear canal and aim the sensor at the eardrum. Once the thermometer is in position, turn it on and wait for an alert to appear indicating the scan is complete. Remove the	Low-grade: 37.3 to 38.0 C (99.1 to 100.4 F) Moderate-grade: 38.1 to 39.0 C (100.6 to 102.2 F) High-grade: 39.1 to 41 C (102.4 to 105.8 F) Hyperthermia: Greater than 41 C (105.8 F)	interval

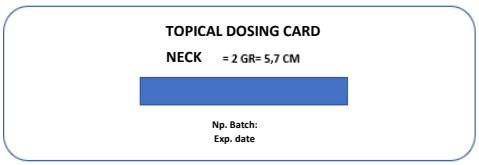
			thermometer from the ear and read the temperature. Average skin temperature will be measured in 5 areas: calf, thigh, abdomen, upper arm and lower neck (near chest). Reference: Mekjavic IB. Life 2021, 11,		
Running duration	The amount of time it takes to complete a 5-kilometer run	Timing device (*stopwatch*)	The researcher calculated the amount of time needed to complete a 5-kilometer run.	Minutes	Numeric al
Average heart rate during a run	Average heart rate during activity	*Heart rate monitor*	The researcher reads the results of the analysis of the subject's *heart* rate data recording on the device connected to the *heart* rate *monitor* used.	Beats per minute	Numeric al
Highest heart rate during a run	Highest heart rate during exertion	*Heart rate monitor*	The researcher reads the results of the analysis of the subject's *heart* rate data recording on the device connected to the *heart* rate *monitor* used.	Beats per minute	Numeric al
Thermal sensation	Assessment of the temperature sensation felt by the subject	*ASHRAE thermal sensation visual analogue ISO 10551*	Subjective assessment of temperature sensation asked directly to the subject based on the scale	7 scale rating score: cold, cool, slightly cool, neutral, slightly warm, warm, hot	ordinal
RPE *(Rating of Perceived Exertion)*	Fatigue perception index	*Borg scale 6-20*	Subjective assessment of fatigue perception asked directly to the subject	6 means no muscle fatigue at all and 20 means maximum muscle effort/fatigue.	ordinal
Perception comfort	Thermal comfort is a satisfaction mind experienced human against conditions temperature in the surrounding environment. Thermal	*ISO 10551*	Subjects were asked to provide a subjective assessment of the level of comfort	5 scale rating score: comfortable, somewhat uncomfortable, uncomfortable, very uncomfortable, extremely	Ordinal

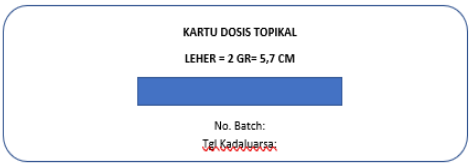
	comfort benchmarks include a balance between temperature air and temperature human body			uncomfortable.	
Irritation	Irritation of the skin to which the test drug is applied	International Contact Dermatitis Research Group (ICDRG) score	The researcher inspects the area where the test drug is applied.		Category

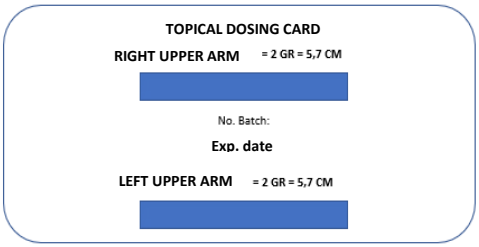
Symbol	Morphology	Assessment
–	No reaction	Negative react
?+	Faint erythema only	Doubtful react
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positi reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reactio

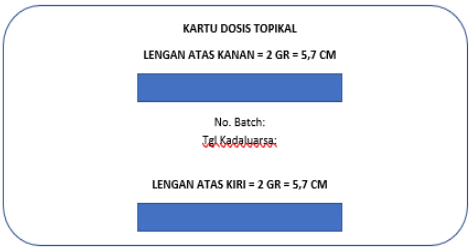
APPENDIX ATTACHMENT

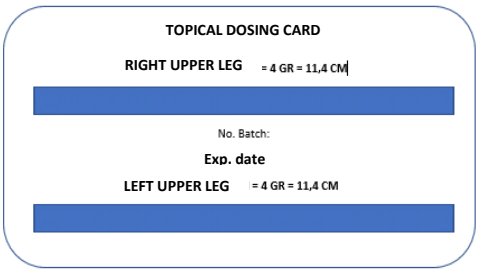
Test Drug Dosing Card

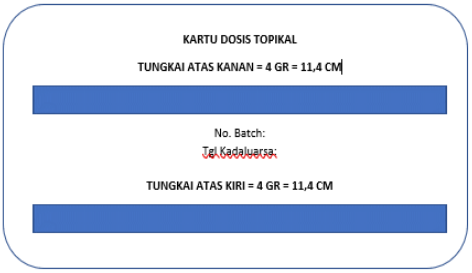


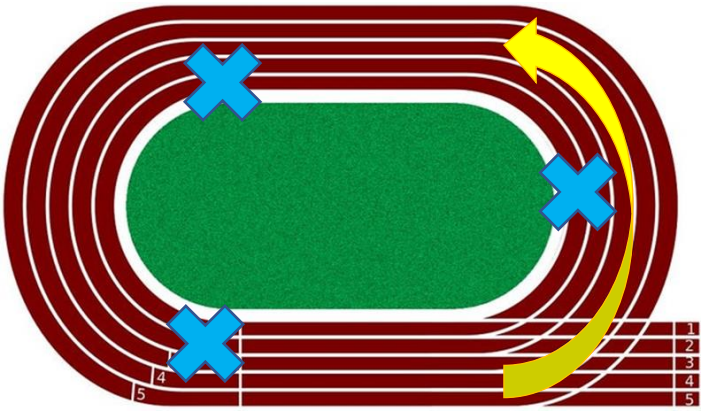












✖ Signaling the administration of the test drug by the Research Coordinator to the Subject

Annex 2. List of other medicines prepared

No.	Equipment/Medicine	Total
1	Topical medication	
	a. Voltaren gel (anti-inflammatory)	1 tube 50 grams
	b. Chloretyl *Spray*	2 cans
	c. Counterpain cream	2 tubes 120 grams
	d. Mofacort ointment (Mometasone furoate 0.1%)	1 tube
2	Wound care	
	a. Betadine antiseptic solution	1 bottle (30 mL)
	b. Sterile gauze	2 boxes
	c. 1-inch micropore	1 piece
	d. Hansaplast plaster	20 pieces
	e. Hansaplast Jumbo Plaster	10 pieces
3	Oral medication	
	a. Diclofenac sodium 25 mg	1 strip
	b. Eperisone HCl	1 strip
	c. Domperidone	1 strip
4	Injectable drugs	
	a. Epinefrine	2 ampoules
	b. Dexamethasone 5 mg/mL	2 ampoules
	c. Sodium chloride infusion solution 0.9%	1 colf (500 mL)
	d. Lactated Ringer's infusion solution	1 colf (500 mL)
5	Miscellaneous equipment	
	a. Oxycan	3 tubes
	b. Ice cubes	1 box/day
	c. Plastic bag with *zip*	1 pack
	d. *Plastic wrap*	1 piece
	e. *Elastic bandage* Tensocrepe 7.5 cm	1 piece
	f. *Elastic bandage* Tensocrepe 10 cm	1 piece
	g. *Elastic bandage* Tensocrepe 15 cm	1 piece
	h. 3 cc syringe	2 pieces
	i. *Alcohol swab*	1 box (100 pieces)
	j. Scissors	1 piece
	k. KN95 Mask	3 *boxes*
	l. *Gloves/handscoon*	1 *box*
	m. AED	1 unit

Appendix 3

VISUAL ANALOG SCORE

Subject Code Number : .....

Day : .....

Date : .....

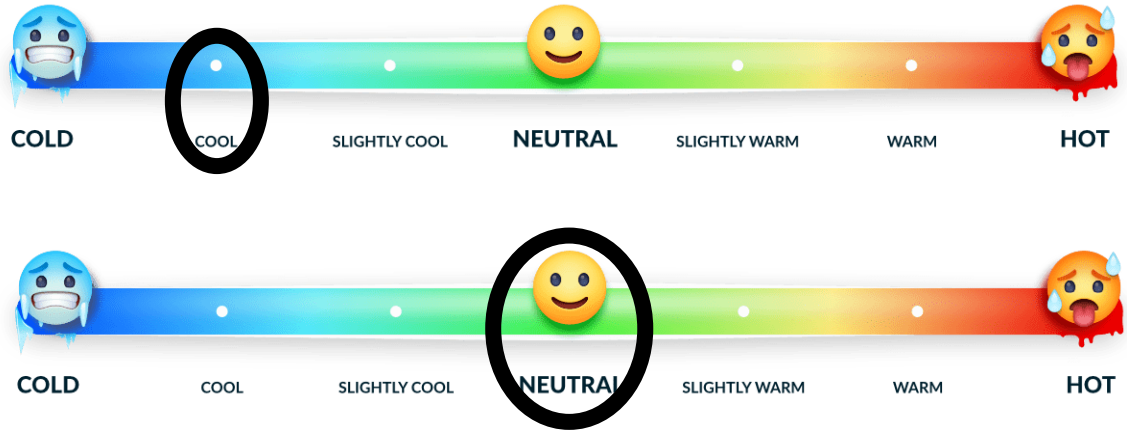
THERMAL SENSATION ANALOG VISUAL SCORE

The following below is a visual analog score to measure thermal sensation after applying the test drug.

Circle the area of the visual analog according to the sensation you feel associated with the application of the test drug at the exact point or image of the visual analog.

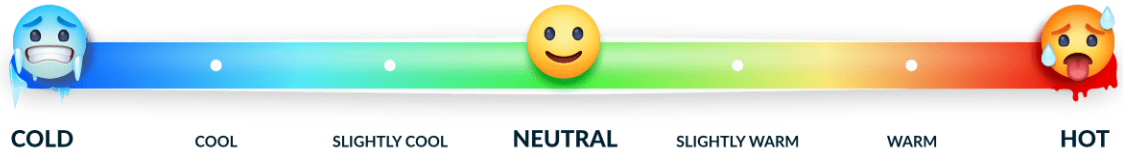
If your form is incorrect, please request a new form.

EXAMPLE:



Filling Sheet

AFTER THE APPLICATION OF THE TEST DRUG, THEN MY CONCLUSION IS:



VISUAL ANALOG SCORE

Subject Code Number : .....

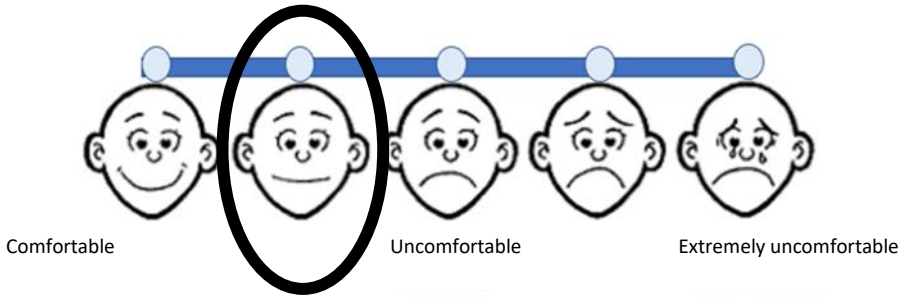
Day : .....

Date : .....

VISUAL ANALOG COMFORT SCORE

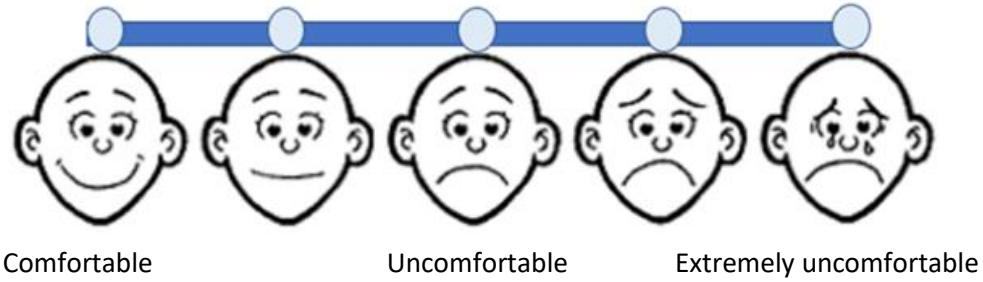
The following below is a visual analog score to measure comfort after applying the test drug. Circle the area of the visual analog according to how comfortable you feel with the application of the test drug on the image of the visual analog.
If your entry is incorrect, please request a new form again.

EXAMPLE:



Filling Sheet

AFTER THE APPLICATION OF THE TEST DRUG, THEN MY CONCLUSION IS:



Appendix 4
Sheet 4
***SCREENING* SHEET FOR PROSPECTIVE SUBJECTS**

Identity

Research Code	
Name (Initials)	
Date of birth	_____ / _____ / _____ (date / month / year)
Age (years)	
Gender	Male/Female*)
Address	
Phone/Mobile	

Interview

Personal best 10 km running duration (minutes)		☐ < 1 hour
Health		
Musculoskeletal injury in the last 3 months	☐ There is:	☐ None
	☐ There are still complaints	☐ No complaints
In the treatment period of chronic diseases (HT, DM, heart disease, etc.)	☐ Yes	☐ No
History of hypersensitivity or allergy to topical products	☐ Yes	☐ No
History of cold allergy	☐ Yes	☐ No
Hijab	☐ Yes	☐ No
Bleep test		
Results	Level:	Balikan:
VO_2max		
	Criteria:	

PAR-Q+ Questionnaire			
This questionnaire was used to confirm the completion of the electronic form previously completed by the Subject.			
SECTION 1 - GENERAL HEALTH			
Please read each question below carefully and answer as honestly as possible. by marking✓ for the appropriate YES or NO answer.			
1.	Has your doctor ever diagnosed you with heart disease OR high blood pressure?	☐ Yes	☐ No
2.	Do you ever feel chest pain at rest, during daily activities, OR during physical activity?	☐ Yes	☐ No
3.	Have you lost your balance due to dizziness OR have you fainted in the past 12 months? Please answer NO if the feeling of dizziness is associated with heavy breathing (including during strenuous physical exercise).	☐ Yes	☐ No
4.	Have you been diagnosed with any chronic/annual health problems (other than heart disease and high blood pressure)?	☐ Yes	☐ No
5.	Are you currently taking any medications prescribed by your doctor for chronic/annual health problems?	☐ Yes	☐ No
6.	Do you have any bone or joint problems that get worse with physical activity? Please answer NO if you have had joint problems in the past, but they do not limit your ability to do physical activity now. For example, knee, ankle, shoulder, or other joints.	☐ Yes	☐ No
7.	Has your doctor told you that you can only do medically supervised physical activity?	☐ Yes	☐ No
If you answered NO to any of the questions above, you are safe to engage in physical activity. If you answered YES to one or more of the above questions, CONTINUE TO PART 2.			

SECTION 2 - CHRONIC HEALTH PROBLEMS			
Please read each question below carefully and answer as honestly as possible. by marking✓ for the appropriate YES or NO answer.			
1	Do you suffer from arthritis, osteoporosis, or back problems?		☐ Yes ☐ No if yes, go to question 1a-1c if not, go to question 2
	1a	Are you having difficulty managing this condition with medication or other therapies from your doctor? (answer NO if you are not currently on medication or other therapies).	☐ Yes ☐ No
	1b	Do you have joint problems that cause pain, recovering from a fracture or fractures due to bone loss (osteoporosis) or cancer, spondylolisthesis, and/or spinal disconnection or fracture of the spine or part of the spine.	☐ Yes ☐ No
	1c	Have you had steroid injections, or taken steroid tablets regularly for more than 3 months?	☐ Yes ☐ No
2	Do you have cancer?		☐ Yes ☐ No if yes, go to question 2a-2b if not, go to question 3
	2a	Do you have any of the following cancers: lung/airway (bronchogenic cancer), multiple myeloma, (plasma cell cancer), head and neck?	☐ Yes ☐ No
	2b	Are you currently undergoing treatment for cancer (e.g. chemotherapy or irradiation/radiotherapy)?	☐ Yes ☐ No

3	Do you suffer from heart disease or vascular disease? Including coronary heart disease, high blood pressure, heart failure, heart rhythm disorders.		☐ Yes ☐ No if yes, go to question 3a-3e if not, go to question 4
	3a	Are you having difficulty managing this condition with medication or other therapies from your doctor? (answer NO if you are not currently on medication or other therapies).	☐ Yes ☐ No
	3b	Do you have any heart rhythm irregularities that require medical attention (e.g. atrial fibrillation, premature ventricular contraction)?	☐ Yes ☐ No
	3c	Do you have chronic heart failure?	☐ Yes ☐ No
	3d	Is your resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know what your resting blood pressure is).	☐ Yes ☐ No
	3e	Have you been diagnosed with coronary heart disease and not engaged in regular physical activity in the past 2 months?	☐ Yes ☐ No
4	Do you have any metabolic problems? Including type 1 diabetes, type 2 diabetes, pre-diabetes.		☐ Yes ☐ No if yes, go to question 4a-4c if not, go to question 5
	4a	Is your blood sugar often higher than 13.0 mmol/L (equivalent to 234 mg/dL)? (Answer YES if you are not sure)	☐ Yes ☐ No
	4b	Do you have signs or symptoms of diabetic complications such as heart or vascular disease and/or complications affecting the eyes, kidneys, and feeling/sensation in the toes and feet?	☐ Yes ☐ No
	4c	Do you have any metabolic problems (e.g. thyroid disorders, diabetes in pregnancy, chronic kidney disease, liver disorders)?	☐ Yes ☐ No
5	Do you have a mental problem or learning disorder? Including Alzheimer's disease, dementia, depression, anxiety disorders, eating disorders, psychotic disorders, intellectual disability, Down syndrome.		☐ Yes ☐ No if yes, go to question 5a-5b if not, go to question 6
	5a	Are you having difficulty managing this condition with medication or other therapies from your doctor? (answer NO if you are not	☐ Yes ☐ No

		currently on medication or other therapies).	
	5b	Do you also have back problems that affect your nerves and muscles?	☐ Yes ☐ No
6	Do you have any respiratory problems? These include chronic obstructive pulmonary disease, asthma, high pulmonary blood pressure.		☐ Yes ☐ No if yes, go to question 6a-6d if not, go to question 7
	6a	Are you having difficulty managing this condition with medication or other therapies from your doctor? (answer NO if you are not currently on medication or other therapies).	☐ Yes ☐ No
	6b	Has your doctor ever stated that your blood oxygen level is low during rest or physical exercise, and/or you need supplemental oxygen therapy.	☐ Yes ☐ No
	6c	If you have asthma, do you currently have symptoms of chest tightness, wheezing, heavy breathing, persistent coughing (more than 2 days per week), or have you used your back-up medication (medication for attacks) more than twice in the last week?	☐ Yes ☐ No
	6d	Has your doctor told you that the blood pressure in your pulmonary veins is high?	☐ Yes ☐ No
7	Do you have a spinal cord injury? This includes paralysis of both arms and legs (tetraplegia) and both legs (paraplegia).		☐ Yes ☐ No if yes, go to question 7a-7c if no, go to question 8
	7a	Are you having difficulty managing this condition with medication or other therapies from your doctor? (answer NO if you are not currently on medication or other therapies).	☐ Yes ☐ No
	7b	Do you often experience very low blood pressure resulting in dizziness, lightheadedness, and/or fainting?	☐ Yes ☐ No
	7c	Has your doctor ever told you that your blood pressure is suddenly high? (known as Autonomic Dysreflexia)	☐ Yes ☐ No
8	Have you ever had a stroke? This includes Transient Ischemic Attack (TIA) or cerebral vascular disorders.		☐ Yes ☐ No if yes, go to question 8a-8c if no, go to question 9
	8a	Are you having difficulty managing this condition with medication or other therapies	☐ Yes ☐ No

		from your doctor? (answer NO if you are not currently on medication or other therapies).	
	8b	Do you have difficulty walking or moving?	☐ Yes ☐ No
	8c	Have you had a stroke or nerve or muscle disorder in the last 6 months?	☐ Yes ☐ No
9.	Do you have any medical problems not listed above, or do you have two chronic/annual health problems?		☐ Yes ☐ No if yes, go to question 9a-9c if not, go to page 5
	9a	Have you experienced blackouts, fainting, or loss of consciousness as a result of a head injury in the past 12 months OR have you had a concussion in the past 12 months?	☐ Yes ☐ No
	9b	Do you have any medical problems that are not listed (e.g. epilepsy/ayan, neurological disorders, renal disorders)?	☐ Yes ☐ No
	9c	Do you currently have two chronic/annual health problems?	☐ Yes ☐ No

Appendix 4

EXPLANATION SHEET TO RESEARCH SUBJECTS

We as a Research Team from Sports Medicine Specialists are conducting research with the title:
Effectiveness of Topical Menthol as an Exercise Cooling Method in a Population of Recreational Runners.

Therefore, at this time, we are providing information about the subject recruitment process to be part of this study.

1. Research objectives

Knowing the effect of using topical menthol application as a cooling method during exercise.

2. Reasons for choosing Mr / Mrs / Brother / Sister

1. 18- 45 years old
2. Have a *personal best* 10 km running time < 1 hour in the last 6 months
3. Doing running training at least 3 times/week for the past 1 year
4. No musculoskeletal injuries (muscle, joint, bone injuries) in the past 3 months
5. No acute infectious disorders such as gastrointestinal infections and respiratory infections
6. Not under treatment for chronic diseases such as hypertension, Diabetes Mellitus, and heart disease
7. No history of hypersensitivity or allergy to gel-based topical products, products containing menthol
8. No history of allergy to cold
9. Not currently infected with COVID-19
10. Not a pregnant or breastfeeding woman

3. Research procedure

Overall, the study process will consist of 2 intervention periods of test drug administration. In the subject recruitment process, you will undergo the following activities:

a. The research team will ask you to confirm the results of the electronic registration form and the PAR-Q questionnaire (physical activity readiness questionnaire).
b. Then, the research team will carry out a physical examination, blood pressure examination, resting ECG examination and current blood sugar and Covid 19 on Mr / Mrs / Brother / Sister.
c. If all tests on the first day are normal, you will be scheduled to take the *Bleep Test* on the second day of screening.
d. On the second day of screening, you will be directed to do static stretching as guided by the Research Team and warm up by running 1 lap (400 m).
e. Mr / Mrs / Brothers / Sisters will be asked for their willingness to do the *Bleep test* to measure the level of pulmonary heart fitness by running from one end or markers cones to the other end or markers cones within 20 meters by following the rhythm of the "beep" sound from the recording tape.

f. If your *Bleep Test* results fall into the minimum sufficient category, then you will be given education and an explanation of the research procedures to be carried out.
g. If all criteria are met, you will receive education related to this study such as: the time of the study day, preparation before running activities, education related to data that will be assessed on the day of the study and actions that need to be reported to the research team.
h. On the first day of the study, the research team will conduct a Covid-19 antigen examination on Mr / Mrs / Brother / Sister.
i. Furthermore, the research team will check your blood pressure before running and you will be given education about the application of the trial materials.
j. Then, you will be asked to take measurements of several parameters, namely weight, height, body mass index, hydration status (by collecting urine in the pot provided), and vertical jump (measuring the height of the jump to measure leg explosive power), followed by body temperature checks at 5 areas and ears.
k. Before doing the running activity, you are directed to do static stretching according to the guidance of the Research Team and warm up by jogging or running for 1 lap (400 m).
l. After that, you will run 5 km as fast as you can.
m. At kilometers 2.5 to 2.8, you will apply the prepared menthol-containing gel or placebo to your neck, right and left upper arms, right and left quadriceps, while continuing to run.
n. After running, you will be measured for body weight, ear temperature, heart rate, vertical jump, fatigue level, temperature sensation and perceived comfort of use and irritation check.
o. You will also be asked to immediately report any complaints or symptoms of health problems or injuries that occur after the study.

4. Risks, side effects and management

There is a risk of injury and *heat related illness* when you run. If this occurs, the screening will be stopped if there are complaints that interfere with the screening process. In addition, the Researcher who is a Sports Medicine Specialist and the Rapid Reaction Medical Team will provide appropriate first aid if there is an emergency condition, in this case contacting the ambulance according to the nearest referral hospital and preparing an AED. If you need further treatment at the hospital, the Sponsor provides insurance that can cover the cost of your treatment.

5. Benefits

The benefit that you can get is a health check and fitness check with a doctor

6. Compensation

There is no special incentive for you to participate in this process. However, the Research Team will provide transportation costs of IDR 300,000 and a reimbursement fee for the time you have given in participating in this study of IDR 300,000 per intervention period. The fee will be provided on the 2nd research day.

7. Confidentiality

All data collected in this study will be kept confidential**.** Presentation of research results at scientific meetings/conferences and publication in scientific journals will not include your name.

8. **Subject Obligations**

   As a Subject, you are obliged to follow the rules or instructions for the screening process of prospective Subjects as written above. If there is anything that is not clear, you can ask further to the research team.

9. **Right to refuse and resign**

   You do not have to participate in this study if you do not want to. And even if you have agreed to participate in this study, you have the right to withdraw from this study at any time.

10. **Additional Information**

    Mr./Ms./Mrs./Brothers/Sisters are given the opportunity to ask all things that are not clear in connection with the screening process of this prospective Subject. If at any time you need further explanation, you can contact Dr. Theresia Indriani Prima Chesar at 081295838147 and Dr. Nisrina Nindriya at 081221734814.

INFORMED CONSENT FORM FOR SUBJECT PARTICIPATION

All these explanations have been provided to me and all my questions have been answered by **_____.** I understand that if I need clarification, I can ask Dr. Theresia Indriani Prima Chesar and Dr. Nisrina Nindriya.

Certificate of *Consent*	
I have read all the explanations about this screening of Subject candidates. I have been given the opportunity to ask questions and all my questions have been answered clearly. I am willing to participate in this research study voluntarily. _____ Subject Name _____ Signature of Subject Tanggal_____ day/month/year	I confirm that participants have been given the opportunity to ask questions regarding this screening of potential Subjects, and all questions have been answered correctly. I confirm that consent has been given willingly. _____ Name of researcher/approver _____ Signature of researcher/approver Tanggal_____ day/month/year

If the Subject is **illiterate*:***
A witness who is not illiterate should sign (if possible, this person should be chosen by the research subject/participant, not his/her parents, and should not have any relationship with the research team). The illiterate research subject/participant must also include his/her fingerprints.

I have witnessed the reading of the *consent* form to the Subject/participant accurately, and have been given the opportunity to ask questions. I confirm that the Subject/participant has given his/her consent freely.

Witness name _____ AND Subject's fingerprints
Witness signature _____
Tanggal _____
date/month/year

Appendix 7

WITHDRAWAL FORM FROM RESEARCH

After reading and listening to the explanation of the research to be conducted by the **Sports Medicine Specialist Research Team** with the title "The Effectiveness of Topical Menthol as a Cooling Method During Exercise in a Population of Recreational Runners" and the information has been well understood by me regarding the benefits, actions to be taken, advantages and possible inconveniences that may be encountered, I:

Name : .....
Age : .....
Gender : .....
Address : .....
Phone No.: .....

I hereby withdraw from the research without any coercion from any party and I will not sue if something happens in the future.

Jakarta, _____

Subject Signature_____ Witness Signature_____
Subject Name: Witness Name: _____

Appendix 7

Research Status

Effectiveness of Topical Menthol as an Exercise Cooling Method in a Population of Recreational Runners

Subject Identity

Sequence number :
Name (Initials) :
Date of birth (Age) :
Gender : Male/Female
Address :
Last education :
Jobs :
Nationality :
Phone No. :
Email address :

Copy of Identification Card (KTP)

☐ Yes
☐ No

Anamnesis

Complaints in the last few months (please mark √)

fever ( ) nausea ( ) vomiting ( ) diarrhea ( ) cough ( ) runny nose ( ) tightness ( ) chest pain ( ) palpitations ( ) cold sweat ( ) others _____

Disease History : Hypertension ( ), Diabetes Mellitus ( ), Heart Disease ( ) Musculoskeletal injury ( )
Allergy History :
Medications being taken:
Exercise routine : ___ Yes. If yes, frequency:
___ No

Fulfillment of Inclusion and Exclusion Criteria

No.	Inclusion Criteria	Yes	No
1	Adults, 18 years old - 45 years old		
2	Have a personal best 10-kilometer run time under one hour (which will be confirmed during the screening of prospective Subjects through history taking) in the last 6 months.		
3	Doing running training at least 3 times/week for the past 1 year		
4	Have a level of heart-lung endurance or VO2max that is at least included in the average criteria (known through examination: Bleep test)		
5	Meets Subject screening criteria by answering "No" to all questions on the Physical Activity Readiness Quesstionnaire (PAR-Q) questionnaire.		
6	Have normal resting ECG and normal GDS results on screening of prospective Subjects.		
7	At the time of the study, the body temperature was within the normal range.		

No.	Exclusion Criteria:	Yes	No
1	Pregnant and/or breastfeeding women		
2	Have had a musculoskeletal injury in the last three months and still have symptoms or complaints		
3	Are experiencing acute infectious disorders, such as gastrointestinal, respiratory infections		
4	During treatment for chronic diseases (e.g. high blood pressure or hypertension, diabetes or diabetes mellitus, heart disease)		
5	Have a history of hypersensitivity or allergy to menthol or skin-applied products (especially gel-based products)		
6	Has a history of cold allergy		
7	Have a Positive Covid-19 test at the time of screening.		

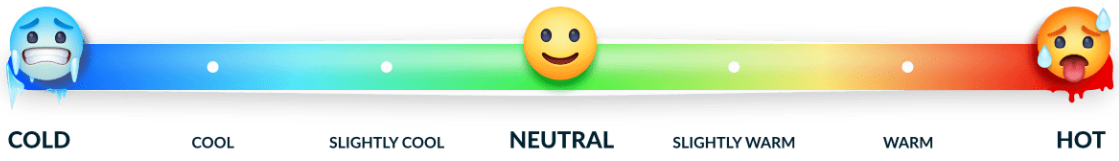
Inspection Result

- Before running

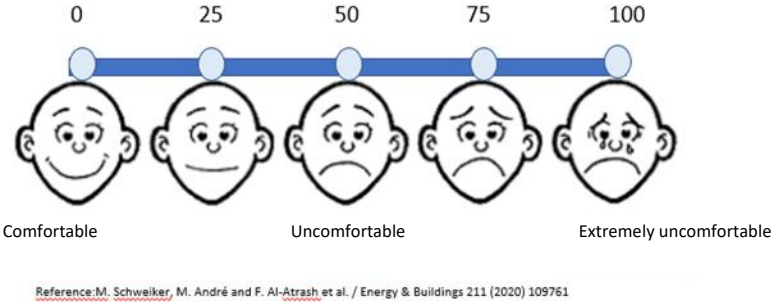
Core body temperature : ºC
Skin surface temperature :
Calves : ºC
Thighs : ºC
Stomach : ºC
Upper arm : ºC
Neck : ºC
Heart rate frequency : times/minute
Blood pressure : mmHg
Body weight : kg
Height : cm
Body mass index : kg/m^2
Vertical jump : cm
Hydration status* :

- After running

Core body temperature : oC
Skin surface temperature :
Calves : oC
Thighs : oC
Stomach : oC
Upper arm : oC
Neck : oC
Max heart rate frequency : times/minute
Average heart rate frequency : times/minute
Blood pressure : mmHg
Body weight : kg
Vertical jump : cm
Hydration status* :
Cold temperature sensation (please circle "O"):



Perceived comfort level (please circle "O"):



Reference:M. Schweiker, M. André and F. Al-Atrash et al. / Energy & Buildings 211 (2020) 109761

Skin Irritation Check:

-	?+	+	++	+++	IR
Negative	Doubtful	Weak Positive	Strong Positive	Extreme Positive	Irritant Reaction

Symbol	Morphology	Assessment
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Appendix 9

ELECTRONIC FORM

Pendaftaran Peserta Penelitian

Kami selaku Tim Peneliti Dokter Spesialis Kedokteran Olahraga sedang melakukan penelitian dengan judul:
EFEKTIVITAS MENTOL TOPIKAL SEBAGAI METODE PENDINGINAN SAAT BEROLAHRAGA DI POPULASI PELARI REKREASIONAL

Pelari rekreasional yang dimaksud adalah pelari yang rutin berlatih lari dengan tujuan untuk meningkatkan kesehatan dan mencari kesenangan dari olahraga lari tersebut, dan bukan memiliki tujuan prestasi.

Tujuan penelitian ini adalah untuk mengetahui pengaruh penggunaan mentol topikal sebagai metode pendinginan saat berolahraga terhadap termoregulasi, performa olahraga & kejadian Delayed Onset Muscle Soreness (DOMS).

Selain identitas, subjek penelitian juga akan mengisi lembar PAR-Q. The Physical Activity Readiness Questionnaire (PAR-Q) merupakan kuesioner yang digunakan untuk mengetahui kesiapan seseorang dalam melaksanakan aktivitas fisik dan latihan fisik, atau apakah seseorang berisiko mengalami masalah kesehatan bila melakukan aktivitas fisik yang lebih berat.

Semua
data yang dikumpulkan dalam penelitian ini akan dijaga kerahasiaannya. Presentasi hasil penelitian dalam
pertemuan ilmiah/konferensi dan publikasi dalam jurnal ilmiah tidak akan mencantumkan nama Bapak/Ibu/Saudara/Saudari.

Harap membaca setiap pertanyaan di bawah ini dengan seksama dan berikan jawaban sejujurnya!

xmastree2512@gmail.com Switch accounts

*Required

Email *

Your email address

Tanggal Lahir *

Date

Nama Lengkap *

Your answer

Jenis Kelamin *

- ◯ Laki-laki
- ◯ Perempuan

Alamat *

Your answer

Nomor Telepon Aktif *

Your answer

Personal best lari 10 km *

- ◯ < 1 jam
- ◯ > 1 jam

Apakah Anda memiliki cedera muskuloskeletal (cedera otot, sendi, tulang) dalam 3 bulan terakhir dan masih memiliki keluhan hingga saat ini? *

- ◯ Ya
- ◯ Tidak

Riwayat Penyakit *

- ☐ Hipertensi
- ☐ Diabetes Mellitus
- ☐ Penyakit jantung
- ☐ Infeksi pencernaan
- ☐ Infeksi pernapasan
- ☐ Alergi dingin
- ☐ Tidak ada
- ☐ Other:

Apakah Anda memiliki riwayat alergi terhadap produk oles (topikal) yang berbahan dasar gel? *

- ◯ Ya
- ◯ Tidak

Apakah Anda menggunakan hijab? *

- ◯ Ya
- ◯ Tidak

Apakah dokter pernah menyatakan bahwa anda menderita penyakit jantung atau tekanan darah tinggi ? *

- ◯ Ya
- ◯ Tidak

Apakah anda pernah merasakan nyeri dada saat istirahat, selama melakukan kegiatan sehari-hari, atau saat melakukan aktivitas fisik ? *

- ◯ Ya
- ◯ Tidak

Apakah anda pernah kehilangan keseimbangan karena pusing atau hilang kesadaran dalam 12 bulan terakhir ? *

- ◯ Ya
- ◯ Tidak

Apakah anda pernah dinyatakan mengidap penyakit kronis/menahun (selain penyakit jantung atau tekanan darah tinggi)? *

- ◯ Ya
- ◯ Tidak

Bila jawaban dari pertanyaan sebelumnya adalah "ya", maka sebutkan nama penyakitnya!

Your answer

Apakah anda saat ini sedang dalam pengobatan karena penyakit kronis? *

- ◯ Ya
- ◯ Tidak

Bila jawaban dari pertanyaan sebelumnya adalah "ya", maka sebutkan penyakit dan nama obatnya!

Your answer

Apakah anda saat ini (atau dalam 12 bulan terakhir) mempunyai masalah pada tulang, persendian, atau jaringan lunak (otot, ligamen, atau tendon) yang bertambah parah dengan melakukan aktivitas fisik? *

- ◯ Ya
- ◯ Tidak

Apakah dokter pernah menyatakan bahwa anda hanya boleh melakukan aktivitas fisik di bawah pengawasan dokter ?

- ◯ Ya
- ◯ Tidak

Submit Clear form

Never submit passwords through Google Forms.